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THE EMOTIONAL AND SOMATIC RESPONSE OF SCHIZOPHRENIC PATIENTS AND NORMAL CONTROLS TO ADRENALIN AND DORYL

BY

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A CONSIDERABLE mass of experimental evidence has been accumulated in recent years indicating the great variability of symptomatology observed in schizophrenic patients (Freeman *et al.*, 1932, 1934, 1935 ; Hoskins *et al.*, 1933 ; Linton *et al.*, 1934 ; Desruelles *et al.*, 1934 ; Whitehorn, 1934 ; Gottlieb and Linder, 1935 ; Marquart, 1935 ; Petroff, 1934 ; Goldstein and Reichmann, 1914 ; Lowrey and Wright, 1920 ; Yoneyama, 1933 ; Gellhorn, 1938 ; McFarland and Goldstein, 1938). This variability serves to call attention to the fact that the term " schizophrenia " embraces a wide range of clinical syndromes. Hoskins *et al.* (1933), Freeman *et al.* (1933, 1934), and Linton *et al.* (1934) have demonstrated the altered activity of the peripheral autonomic nervous system in schizophrenic patients, with a failure to maintain the homeostatic mechanisms. On the other hand, Myerson *et al.* (1937, a, b, and c ; 1938) have employed schizophrenic patients to carry out an important series of tests to determine the pharmacological action of various drugs having an action similar to that of the autonomic nervous system. Their results would indicate that the peripheral activity of the autonomic nervous system as tested on schizophrenic patients was little different from that obtained by other investigators, using different controls (Starr, 1933 ; Starr *et al.*, 1933 ; Fraser, 1938). It has long been known that schizophrenic patients showed a physiological as well as a psychological dissociation. Bowman and Kasanin (1929) and later Whitehorn (1934) demonstrated that there was no correlation between the mood of the patient and the degree of fasting glycæmia. This finding was more or

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less at variance with Cannon's work with animals, which demonstrated that such reactions as rage and fear brought an increase in the output of adrenalin, a rise in blood sugar, and a glycosuria. Gildea *et al.* (1935) demonstrated that normal individuals under intense emotional stress developed a rise in blood sugar, again indicating a difference or variation from the observations made on schizophrenic patients, and tending to substantiate the work done on animals. Cori and Buchwald (1930) demonstrated that the vascular response in man is much more sensitive to adrenalin than in the common laboratory animal, indicating that there were probably both qualitative and quantitative differences between various autonomic mechanisms in man and in animals which made comparisons between them difficult.

Recently Lindemann and Finesinger (1938) used adrenalin and mecholyl to induce or reactivate the anxiety states of a group of psychoneurotic patients. They were more interested in the verbal report of the patient and his behaviour, following the use of these drugs, than in the evidence of peripheral activity, and give no series of normal controls receiving the same drugs. It is of considerable interest, however, to find that all of their patients except one had a typical anxiety attack induced by either adrenalin or mecholyl or by both drugs. This single exception is of particular interest as this patient seems to have been suffering from a schizophrenic-like mental illness. This raises two questions : How would a group of normal individuals respond to injections of these drugs, and how would a group of emotionally deteriorated schizophrenic patients respond to the same drugs ? As has been indicated previously, this type of investigation has been carried out before, although the investigator's attention was primarily centred on the peripheral activity of the autonomic nervous system and not on the emotional response.

Method

Instead of dealing exclusively with the peripheral autonomic response of schizophrenic patients to various autonomic stimulants, we have attempted to correlate the patient's emotional response with the peripheral response, comparing it with a group of normal controls. The schizophrenic patients chosen for this investigation were co-operative individuals, capable of responding to direct questioning and having no gross physical abnormality. There were 10 patients selected (five men and five women). The average age of the group was 31 years. The average duration of the psychosis was 9 years. There was either marked poverty of affective response or an inappropriate affective response in each patient with evidence of emotional deterioration. Seven of the 10 had previously been given either insulin shock or convulsant drug therapy without improvement. There were six individuals in the normal control series (four men and two women), all recruited from a general surgical service. Two of the men were convalescing from an operation for hernia, and the remaining four patients were convalescing from chronic tuberculous lesions of bone, being in good physical condition otherwise and having no other demonstrable abnormality. The average age of the control group was 26 years.

None of the control group showed any abnormal mental symptoms and all were emotionally stable.

The investigation was carried out on both the schizophrenic and the normal control group in the morning. These patients were allowed no breakfast or sedatives, as it has been demonstrated that sedatives produce a definite alteration of glucose metabolism (Tod, 1935). The patients remained quietly in bed for at least 30 minutes before the tests were begun. Each patient was asked, " How do you feel ? " If there were no complaints or symptoms of anxiety or apprehension, blood pressure and pulse rate were taken and a neurological examination was carried out, with special reference to the activity of the autonomic nervous system (e.g. sweating, pallor, flushing, salivation, lachrymation, peristalsis, or urgency). A sample of venous blood was taken from the patient and immediately following 1 c.cm. of normal saline solution was injected intramuscularly. At the end of 15 minutes the patient was asked, " How do you feel now ? " and then, " Have you noticed any change ? " If the patient made no spontaneous comment as regards his emotional reactions he was asked, " Have you felt nervous, apprehensive, or fearful ? " Venous blood was again withdrawn 15 minutes after the saline injection, and another neurological examination carried out. The patient was then given either adrenalin or doryl (carbaminoylcholine chloride) intramuscularly. The former was given in doses of 0·5 to 1 c.cm. of a 1 to 1,000 solution and the latter in doses of 10 to 20 mgm. (1 to 2 c.cm.), and again venous blood was withdrawn (at 15 min. and 1 hour following), a neurological examination was carried out, and a record made of the patient's behaviour and spontaneous comments, as well as his answers to questions.

Results

The results of this investigation as regards blood-sugar determinations, pulse rate, blood pressure, and pulse pressure are recorded in the following tables. The figures represent the average of the maximum rise or fall of the particular item under investigation, giving a comparison of the reaction of the schizophrenic group with that of the control group. It might be stated that there was no significant somatic or psychic reaction in either group following the injection of normal saline.

TABLE 1.—ADRENALIN

INDICATOR	BLOOD SUGAR		PULSE RATE		BLOOD PRESSURE		PERCENTAGE RISE PULSE PRESSURE	
Dose of adrenalin ..	0·5 c.c.	1 c.c.	0·5 c.c.	1 c.c.	0·5 c.c.	1 c.c.	0·5 c.c.	1 c.c.
Schizophrenic	+23	+66	+20	+21	+14	+23	+40	+122
(Range) ..	(+1 to +53)	(+46 to +118)	(−4 to +34)	(−8 to +52)	(+8 to +20)	(−10 to +52)	(+17 to +72)	(+70 to +186)
Normals ..	+43	+47	+12	+16	+15	+29	+128	+92
(Range) ..	(+16 to +71)	(+6 to +92)	(+4 to +20)	(+12 to +20)	(+10 to +20)	(+25 to +30)	(+82 to +175)	(+73 to +114)

Table 1 shows the response of the schizophrenic and normal control groups to 0·5 c.cm. and 1 c.cm. of adrenalin given intramuscularly. The range of response is indicated by the figures in brackets, and as might be expected there was considerable individual reaction. There tends to be a somewhat wider range and more variability of response in the schizophrenic group than in the normal control group, although this difference is not invariably striking.

TABLE 2.—DORYL

INDICATOR	BLOOD SUGAR		PULSE RATE		BLOOD PRESSURE		PERCENTAGE RISE PULSE PRESSURE	
Dose of Doryl ..	1 c.c.	2 c.c.	1 c.c.	2 c.c.	1 c.c.	2 c.c.	1 c.c.	2 c.c.
Schizophrenic (Range) ..	−3 (−15 to +25)	−8 (−18 to 0)	−2 (−24 to +10)	+5 (−8 to +16)	−14 (−30 to +10)	−20 (−30 to +5)	−3 (−18 to +22)	−3 (−40 to +30)
Normals .. (Range) ..	−1 (−9 to −2)	−5 (−2 to +6)	−3 (−12 to +4)	−5 (−16 to +8)	−5 (−7 to +5)	−1 (−12 to +5)	0 (−4 to +9)	+1 (−11 to +9)

In spite of the fact that these indicators show so little reaction after doryl, the general peripheral action of the drug, as evidenced by flushing, sweating, lachrymation, increased peristalsis, and urgency of urination were all quite marked in both groups. If anything, the peripheral action of the drug was more noticeable and intense in the schizophrenic group.

The most significant feature of this investigation is the emotional reaction or lack of reaction. As previously stated, the schizophrenic group of patients in this series were selected primarily on the basis of their lack of affective response, or inappropriate affective reaction, of long standing, the average duration of psychosis being 9 years. The control group, on the other hand, were convalescent post-operative patients with no nervous or mental complaints and with quite an appropriate emotional response. Invariably and without exception each individual in the normal control group experienced some degree of anxiety, apprehension, or fear following the intramuscular injection of adrenalin. This occurred in those receiving 0·5 c.cm. as well as those receiving 1 c.cm. These members of the control group complained spontaneously of palpitation, a feeling of tension and substernal constriction, a vague and indefinite but very real anxiety, which lasted only for a few minutes and was followed by a feeling which most of them described as being " nervous, jumpy, and on edge." None of the control group had ever felt quite the same way before. Trembling and facial pallor were common reactions in this group. There was no aggressive behaviour exhibited by any member of the control group. In four of this group all subjective symptoms had subsided at the end of 1 hour. In two of the control group, symptoms of nervousness persisted for about 5 hours and culminated in a mild headache.

This general reaction in the control group following adrenalin is in striking contrast to the reaction of the schizophrenic group following the intramuscular injection of adrenalin. There was not a single schizophrenic in the entire group of 10 patients whose behaviour, spontaneous response, or verbal report on direct questioning indicated anything which could be interpreted as an anxiety reaction. There was no change in the individual patient's apathetic or inappropriate emotional response. There was no aggressive behaviour. A few of them laughed and talked to themselves or to imaginary companions, but invariably when questioned there was never any indication of apprehension, anxiety, or fear. In fact, the schizophrenic patients did not complain of palpitation, although it was quite obvious that their hearts were beating very forcibly and rapidly. The indicators of autonomic response as summarized in Table 1 show quite an adequate response in the schizophrenic group. Trembling and facial pallor were also observed in the schizophrenic group. This adequate peripheral response had no emotional counterpart such as was so plainly evident in the control group.

The normal control group showed no emotional reaction to intramuscular injections of doryl in either 10 or 20-mgm. doses. As previously stated, the peripheral response in each instance was not unusual. No aggressive behaviour was noted and no " panic " reaction as described by Lindemann and Finesinger (1938) was observed. The schizophrenic group likewise showed no evidence of emotional reaction to doryl in spite of an even more active peripheral autonomic response than was noted in the control group. Each patient remained placid and unperturbed. One schizophrenic patient stated that he had a pleasantly warm sensation over his body after receiving 20 mgm. of doryl. When questioned specifically not one of the schizophrenic patients admitted any anxiety or fear reaction at any time.

It is realized that the action of doryl on the cardiovascular mechanisms is less marked than the action of mecholyl used by Lindemann and Finesinger (1938) in their series. This may account for the fact that no anxiety reactions were experienced by either group, although under the circumstances one could not expect any more reaction in the schizophrenic group than was observed following adrenalin. It is, of course, realized that the complex emotional derangement observed in schizophrenia is not completely explained by the failure of this group to react emotionally to adrenalin. Other investigators have observed alterations in the peripheral autonomic response in schizophrenic patients, but have not stressed the failure of various autonomic stimulants to arouse in the schizophrenic those same emotions experienced by normal individuals. From the physiological side it has been demonstrated that the adaptive mechanisms of the schizophrenic to preserve the " steady state " (Cannon, 1935) are defective under stress. Bard and Rioch (1937) have demonstrated in animals that the cerebral cortex was not necessary for the regulation of emotional expression, and indicated the importance of the hypothalamus in preserving an appropriate emotional response. Haškovec (1925, 1929) has contributed to the literature in this respect as regards derangement of emotional expression observed in patients with lethargic encephalitis, tumours

of the hypothalamus, narcoleptic seizures, catatonic states, toxic conditions, drugs, etc. Recently Smyth and Stern (1938) have reported on the mental deterioration resulting from tumours arising primarily in the thalamus. Haškovec (1929) and Nathan (1931) are of the opinion that the cortex plays no essential part in the regulation of the individual's affective life, and believe that the nuclei in the walls of the third ventricle are of the utmost importance in the regulation of the individual's affective dispositions. Singer (1938) concludes that the presence of a psychosis always indicates a disturbance of central autonomic integration, although this would appear more speculative than based on sound experimental data. Papez (1937, 1939) takes a somewhat broader and less dogmatic view, recognizing the importance of the hypothalamic and paraventricular nuclei, but at the same time stressing the cortical connections of these various centres. It is not within the scope of this paper to discuss the anatomy and physiology of the thalamus or hypothalamic centres. The work of Head (1918, 1920), Head and Holmes (1911), Ranson (1937), and recently Fulton (1938), Walker (1938), Le Gros Clark *et al.* (1938), may be referred to, as well as the excellent summary articles by Papez (1937, 1939). The demonstration of a failure of large doses of adrenalin to arouse any evidence whatever of emotional response in a group of schizophrenic patients as compared with a group of normal controls would favour the opinion that the inappropriate emotional response in schizophrenic patients is at a physiological level as contrasted with the view held by many that a psychological explanation will account for the inappropriate emotional response observed in these patients. In view of the adequate peripheral autonomic response in the schizophrenic group, it would appear that the break in the chain of reactions was not at that point. Beyond these observations of the failure of the schizophrenic patients to respond with appropriate emotional response to adrenalin, we have no experimental evidence which localizes the actual site of the difficulty, and are aware of no other experimental work on human patients which demonstrates the part of the nervous system involved in this disorder. It might be suggested that the central autonomic connections were disturbed in schizophrenia. We present only indirect evidence of such disorder, which must await further direct confirmation.

Conclusions

Emotional and somatic reactions of schizophrenic patients and normal controls are compared following intramuscular injection of adrenalin and doryl.

No significant difference was noted in the somatic response of the two groups, although the schizophrenic group exhibited more variability of response to both adrenalin and doryl, tending to bear out the findings of others to the effect that the adaptive mechanisms of the schizophrenic to preserve the " steady state " are defective under stress.

Doryl injected intramuscularly produced an excellent peripheral autonomic

response in both the schizophrenic and normal groups, but no emotional disturbance (anxiety or fear) in either group.

The clear-cut and definite failure of adrenalin to arouse anxiety or fear response in the schizophrenic as compared with the normal control group is significant, and points to a disordered emotional mechanism at a physiological level. We present experimental data which only indirectly localize this break in the chain of physiological response, and all explanations are highly speculative.

No claim is made of the efficacy of using adrenalin to differentiate schizophrenics from other mental disorders by means of their emotional response, although the findings reported would suggest possibilities for investigation in an effort to understand better the central emotional mechanism.

We are indebted to Professor D. K. Henderson for placing the facilities of the Royal Edinburgh Hospital at our disposal, and also to Dr. Colin Campbell, Mr. Wm. C. Wilson, and Mr. C. F. W. Illingworth of the Surgical Department of the University of Edinburgh for securing a control group of patients.

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THE DISTRIBUTION OF COMMISSURAL FIBRES IN THE CORPUS CALLOSUM IN THE MACAQUE MONKEY

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DURING an investigation to determine the projection of the cerebral cortex on to the pons and cerebellum by tracing fibres undergoing Marchi degeneration, a series of cortical lesions was made in macaque monkeys. In the preparation of this material for histological examination, the corpus callosum was sectioned to see which of the cortical areas studied gave origin to commissural fibres and to determine the relative position of these in the corpus callosum. Though the presence of callosal fibres is often recorded in contributions dealing with experimental studies on cortical projectional pathways, their position in the corpus callosum is not often referred to.

The observations are based on six experiments. The lesions were localized, so as to involve, as far as possible, not more than two cyto-architectural areas. They were produced by the method of devascularization, already described in a previous paper, which is based on the principle that, if the superficial pial vessels to a cortical area are obliterated, the cortex undergoes complete necrosis, while the changes in the subjacent white matter are, in general, restricted to that portion of it which is occupied predominantly by fibres arising in the involved cortex (Sunderland, 1938). In this method of devascularization, subjacent fibre pathways are thus likely to be preserved intact, and this is particularly important since it is essential that any fibre tracts of a possible commissural nature from adjacent cortical areas should be avoided.

The animals were anæsthetized by means of the intra-peritoneal injection of sodium ethyl barbiturate (nembutal), using 0·7 c.c. of a 5 per cent. solution per kilogram of body weight. In each case the left cerebral hemisphere was exposed by reflecting a rectangular osteo-plastic flap, and the lesion produced as described. After all bleeding had been carefully controlled the wound was closed. There were no post-operative complications. The animals were killed 17 days later by ether anæsthesia. The vascular system was perfused with 10 per cent. formalin after clearing it with repeated washings with normal saline by way of the aorta. The brain was removed 1 hour later, washed in

running water, and the corpus callosum then exposed and removed. The block of tissue was mordanted in potassium bichromate and then passed through potassium bichromate containing various quantities of osmic acid, cleared in spirit, and finally embedded in celloidin. Sections were cut at 15μ. The cortical lesions were carefully examined, measured, and drawn.

Experimental results

Experiment 1.—Monkey 45A. Operation 5th May, 1938. Killed 23rd May, 1938.

The lesion was situated in the prefrontal region involving most of area 8, but also encroaching on areas 9 and 10. It measured 17 mm. coronally and 15 mm. sagittally. The anterior margin was 12 mm. from the frontal pole,

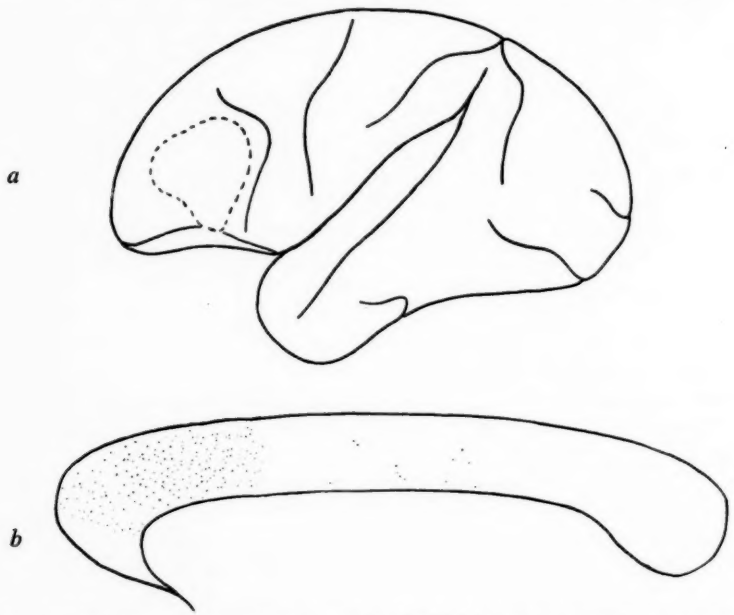

Fig. 1.—The lesion in experiment 1 and the distribution of the degenerated fibres in the corpus callosum.

while the posterior margin traced a parallel course 3 mm. anterior to the sulcus arcuatus. Inferiorly it just reached the lower margin of the brain (Fig. 1, *a*).

In the sections of the corpus callosum fine Marchi granules were distributed evenly over the genu and the anterior third of the body, being densely arranged in the posterior part of this area. A few isolated granules were also seen elsewhere in the body, chiefly along its inferior aspect, but these were widely scattered and of doubtful significance. There was no Marchi deposit in the anterior commissure (Fig. 1, *b*).

Experiment 2.—Monkey 46A. Operation 29th June, 1938. Killed 16th July, 1938.

The lesion was situated at the lower end of the upper limb of the sulcus lunatus and involved parts of areas 17, 18, and 19. The end of the sulcus was included in the lesion, the latter measuring 18 mm. anteroposteriorly and 14 mm. in a vertical direction. Anteriorly the margin reached almost to the temporal sulcus, while it was 24 mm. from the occipital pole posteriorly and 7 mm. from the lower border of the brain inferiorly (Fig. 2, *a*).

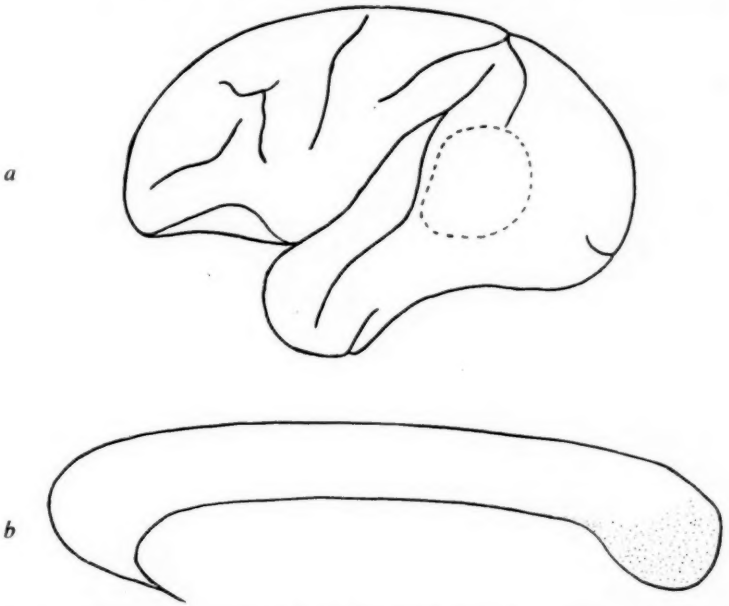

Fig. 2.—The lesion in experiment 2 and the distribution of the degenerated fibres in the corpus callosum.

In the corpus callosum a deposit of fine Marchi granules was scattered over the splenium in an open and irregular manner, with a small extension anteriorly along the neighbouring inferior border of the body. The splenial deposit was slightly more extensive and pronounced than that observed in the splenium in experiment 4. There was no Marchi deposit in the anterior commissure (Fig. 2, *b*).

Experiment 3.—Monkey 47A. Operation 24th June, 1938. Killed 13th, July, 1938.

The lesion involved the upper part of the post-central gyrus, including areas 5, 2, and 1. It measured 17·5 mm. sagittally and 13 mm. coronally. The upper margin of the lesion was 5 mm. from the superior border of the brain. Anteriorly the lesion just reached the sulcus centralis, while posteriorly it

extended along the intraparietal sulcus. Neither sulcus was damaged (Fig. 3, *a*).

There was an even and dense deposit of large Marchi granules in the posterior third of the body of the corpus callosum, and a much fainter deposit more anteriorly in approximately the middle third, where, however, the few granules present were irregularly scattered, with a suggestion of concentrations along the upper and lower margins of the body about its centre. There was no Marchi deposit in the anterior commissure (Fig. 3, *b*).

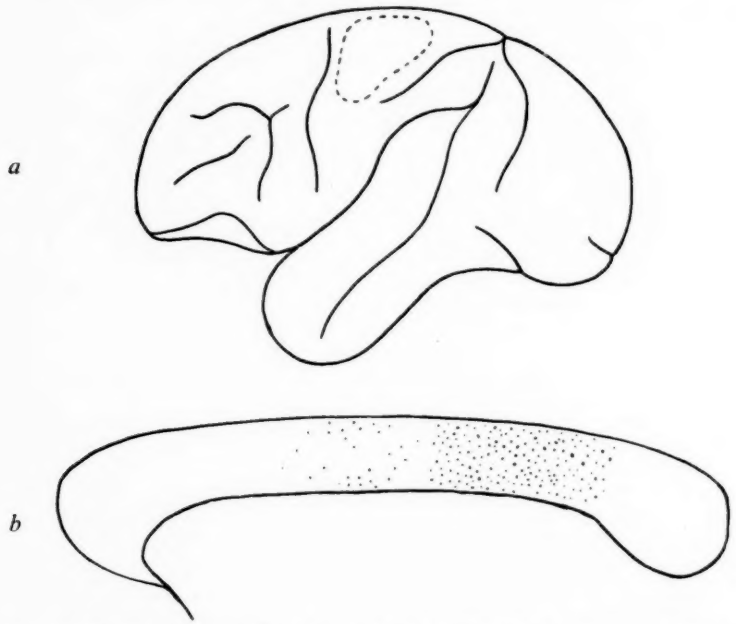

Fig. 3.—The lesion in experiment 3 and the distribution of the degenerated fibres in the corpus callosum.

Experiment 4.—Monkey 49A. Operation 12th May, 1938. Killed 30th May, 1938.

The lesion was an extensive one involving most of the outer surface of the occipital lobe. It measured 28 mm. coronally and 14 mm. antero-posteriorly. The margin of the lesion was 15 mm. from the occipital pole posteriorly and 5 mm. and 3 mm. from the inferior and superior borders of the brain respectively. Anteriorly it followed the sulcus lunatus, but remained separated from it by a distance of 1 mm. The lesion involved area 17 and the immediately adjacent part of area 18 (Fig. 4, *a*).

Large Marchi granules were observed in the septum pellucidum, at the junction of the posterior third and anterior two-thirds of the body, and a finer deposit in the splenium of the corpus callosum. In the septum the granules

were clustered anteriorly and posteriorly, and their arrangement suggested that they were located in fibres directed anteroposteriorly across the septum. The granules were openly and irregularly distributed over the tip and lower aspect of the splenium, with an extension of more densely arranged granules reaching forwards for a short distance along the lower margin of the body. The small patch of the body was well separated from the other deposits. There was no Marchi deposit in the anterior commissure (Fig. 4, *b*).

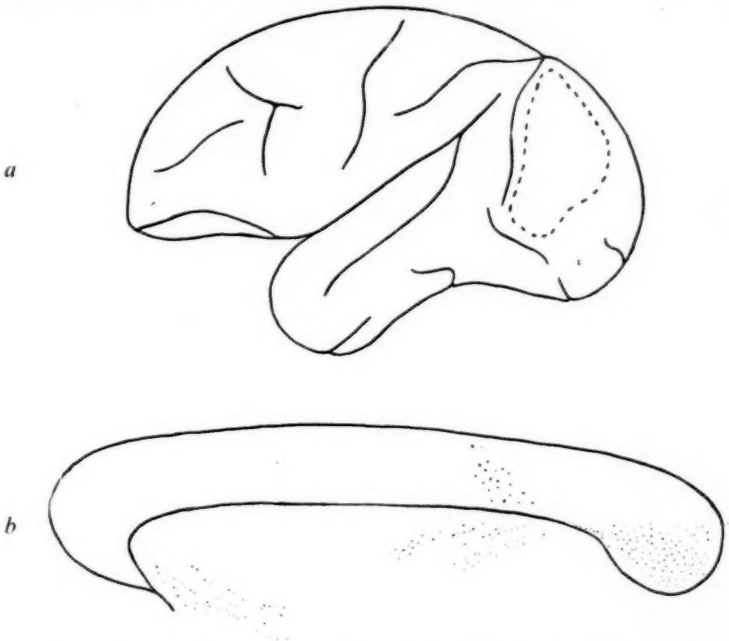

Fig. 4.—The lesion in experiment 4 and the distribution of the degenerated fibres in the corpus callosum.

Experiment 5.—Monkey 50A. Operation 24th May, 1938. Killed 10th June, 1938.

The lesion was located in the prefrontal region above the sulcus arcuatus, the upper extremity of which was involved in the lesion. The latter involved areas 6 and 9. Its dimensions were 19 mm. antero-posteriorly, with a maximum coronal diameter of 12 mm. Antero-inferiorly the margin of the lesion was in contact with the sulcus rectus, while superiorly a distance of 5 mm. separated it from the superior border of the brain (Fig. 5, *a*).

There was a heavy deposit of fine Marchi granules distributed evenly over the genu and a little more than the anterior third of the body of the corpus callosum. Posteriorly this deposit thinned away abruptly over the middle third of the body, where, in comparison, the granules were much fewer in number and more openly arranged. The deposit in the anterior third of the

body was more extensive and the granules more closely packed than in experiment 1. There was no Marchi deposit in the anterior commissure (Fig. 5, *b*).

Experiment 6.—Monkey 52A. Operation 26th May, 1938. Killed 13th June, 1938.

This lesion measured 16 mm. in length and 10 mm. in width. It was situated in the inferior portion of the superior temporal gyrus, but did not involve the Sylvian fissure or temporal sulcus. It was localized to area 22 (Fig. 6, *a*).

The main Marchi deposit, in the form of large granules, was spread over the

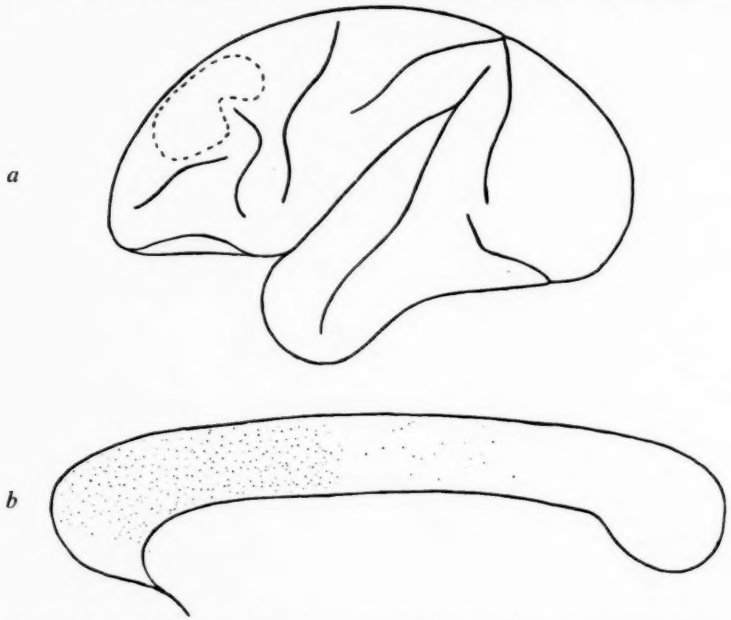

Fig. 5.—The lesion in experiment 5 and the distribution of the degenerated fibres in the corpus callosum.

middle third of the body of the corpus callosum. Isolated granules were also diffusely scattered over the posterior third, where, in addition, there was a linear concentration of granules along the lower margin. In this case the anterior commissure showed a definite deposit in the form of large Marchi granules scattered diffusely over the rostral half of the commissure (Fig. 6, *b*).

Discussion

Current statements regarding the distribution of commissural fibres in the corpus callosum mostly have as their basis the observations of Mingazinni (1926), whose studies on the myelination of fibres in the corpus callosum of the human brain showed that frontal fibres cross by way of the genu, that the

body contains fibres from the first frontal, precentral, parietal, paracentral, and insular territories, while parietal, occipital, lingual, and angular fibres are confined to the splenium. The observations made in this experimental investigation on the monkey's brain are not entirely in accord with Mingazinni's observations on the human brain. While it is probable that the two are not closely comparable, because of the different degree of relative development of some of the cortical areas, it also appears that the experimental method is likely

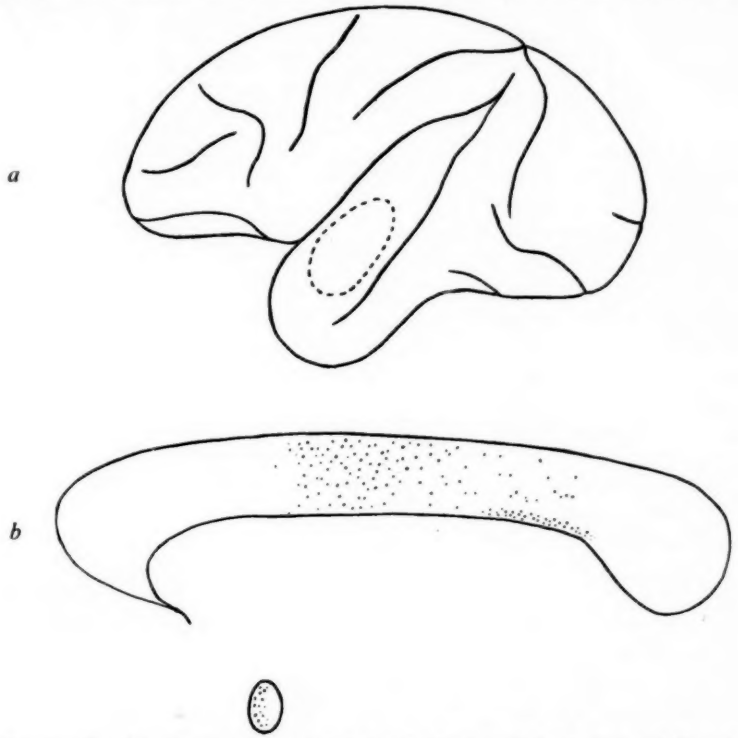

Fig. 6.—The lesion in experiment 6 and the distribution of the degenerated fibres in the corpus callosum.

to yield more precise information regarding the location in the corpus callosum of commissural fibres from different cortical areas.

All the cortical lesions which were made gave origin to a degeneration of callosal fibres. Since each lesion involved, except in the case of experiment 6, a group of cyto-architectural areas, it is impossible to assess with any accuracy the relative contribution from each particular area.

Callosal fibres from the frontal lobe occupy approximately the genu and the anterior third of the body of the corpus callosum, and the nature of the deposit suggests that a proportionately large number of commissural fibres arise in the frontal areas. In experiment 5, the smaller of the two frontal lesions,

the deposit was denser and occupied a slightly more extensive area than in experiment 1, and this is perhaps due to the preponderance of commissural fibres coming from the premotor area. The deposit in the splenium was very similar in the two experiments involving the occipital cortex, though in experiment 4 it was not restricted to this portion of the corpus callosum. The amount of the deposit observed in the two cases suggests that more commissural fibres in the splenium arise from the peristriate areas than from the striate area. It is generally believed (Valkenburg, Poliak *et al.*) that area 17 gives no commissural fibres, and, if this is true, the large number of callosal fibres in experiment 4 must arise in the small strip of area 18 which is presumably included in the lesion. It should be noted, however, that Poliak (1927) has demonstrated that callosal commissural fibres arise from the area striata in the cat. The surface area of the lesion in experiment 2 exceeds that belonging to area 18 in experiment 4, and the inference drawn from this observation is that area 19 is not represented in the corpus callosum to the same extent as area 18. If the area striata is eliminated, the splenial fibres revealed in this study presumably take origin in areas 18 and 19. It is difficult to comment on the nature of the fibres occupying the posterior third of the body of the corpus callosum and the septum pellucidum. Though they are well separated from the remainder they presumably take origin in area 18 ; perhaps they represent fibres of a heterotopic type which are directed more anteriorly than the others.

In both the temporal and parietal lesions there was a heavy deposit scattered irregularly over the posterior two-thirds of the body of the corpus callosum, but the patches where the granules showed a relative concentration differed in two lesions and suggest that the main mass of fibres from the temporal lobe occupy a position in the corpus callosum anterior, though not inferior, to those coming from the parietal lobe. In the case of the temporal lesion additional commissural fibres were observed to cross by way of the anterior commissure. It seems certain that these fibres come from the temporal cortex, because in this series the lesions were localized to the cortex, and this would exclude any damage to the basal ganglia or subjacent fibre tracts in this case, an explanation which is believed by some to account for the deposit in the anterior commissure following temporal lesions.

Comparing the size of the lesions and the amount of the deposit in each experiment it appears that, so far as the regions studied here are concerned, the parietal lobe gives origin to most commissural fibres and is followed by the frontal, temporal, and occipital territories in that order ; and that, while parietal and temporal fibres are spread over a greater area of the corpus callosum, those coming from the frontal lobe show a greater concentration. An interesting point is the extensive callosal areas over which fibres from relatively small cortical regions are dispersed. In general, the frontal fibres occupy the genu and anterior third of the body and the occipital fibres the splenium. In the middle third, frontal, parietal, and temporal fibres overlap, with the latter predominating, while parietal, temporal, and occipital fibres are distributed over the posterior third in that order of importance.

From the distribution of the deposit it appears that localization in the

corpus callosum is of a very general type. Not only are the commissural fibres from some cortical areas diffusely spread over the corpus callosum, but there is also an overlap of fibres coming from different areas in the same lobe, and also, apparently, from areas in different lobes (Fig. 7).

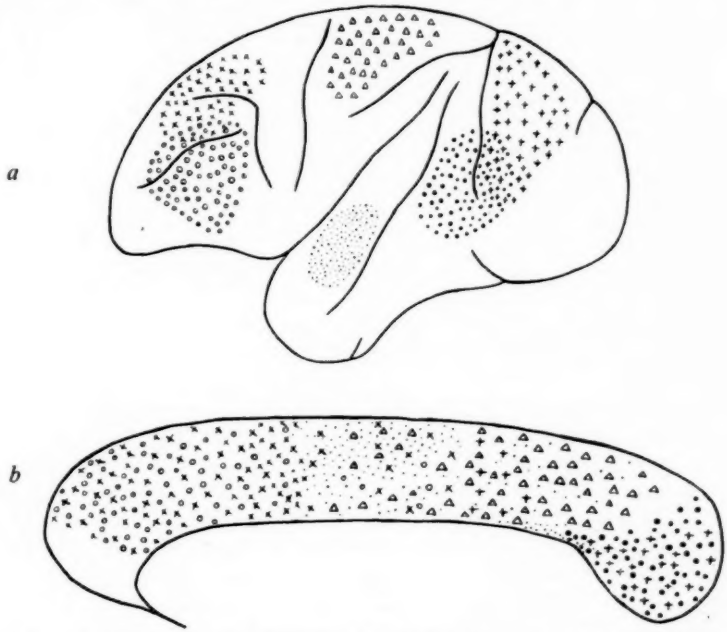

Fig. 7.—Diagram illustrating the degree of overlap in the corpus callosum of fibres coming from different cortical areas.

Summary

The presence and situation of commissural fibres in the corpus callosum, as shown by a study of degenerating fibres following cortical lesions, are described.

Areas studied in the frontal, parietal, occipital, and temporal lobes were all found to contribute to the callosal system.

The position occupied by the fibres is discussed, with the general conclusion that the frontal fibres are spread over chiefly the genu and anterior third of the body, with some occupying the middle third, the occipital over the splenium and posterior third of the body, and the parietal and temporal over the posterior two-thirds of the body with those from the temporal occupying a position anterior to those coming from the parietal. The existence of commissural fibres from the temporal lobe crossing by way of the anterior commissure is confirmed. The amount of the Marchi deposit recorded suggests that, from areas of equal extent, the parietal cortex contributes relatively the greatest

number of commissural fibres, and then the cortex of the frontal, temporal, and occipital lobes in that order.

It is a pleasure to acknowledge the advice and assistance which Professor Le Gros Clark has so kindly placed at my disposal throughout the investigation.

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BEHAVIOUR AND MOOD CYCLES APPARENTLY RELATED TO PARATHYROID DEFICIENCY

BY

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INCREASING interest in the cyclic behaviour of man and animals has been evidenced in recent years, especially in so far as these cyclic changes are related to glandular disturbances.

In studies of the spontaneous activity of rats the following cycles have been observed : a 4–5-day cycle associated with ovulation (Wang, 1923) ; a 14-day cycle after section of the pituitary stalk (Richter, 1933) ; a 15–20-day cycle after parathyroidectomy (Richter and Eckert, 1937) ; a 25–35-day cycle after thyroidectomy (Richter, 1933) ; and a 100-day cycle after removal of one ovary and all except a small part of the other ovary (Richter, 1927). Hitherto, in other animals and in humans the only cycles definitely known to depend on endocrine glands were the ovulation and menstrual cycles. In humans with pathological disturbances we know of several other cycles, but we have no knowledge regarding their origin : (1) the morning-evening variations in mood seen particularly in depressions ; (2) a 2-day cycle of alternating good and bad days of behaviour and sleep found in manic-depressive patients (Richter, 1938) ; (3) a 4–6-day cycle manifested in sleep (Richter, 1934) ; and (4) a 9–11-day cycle manifested in attacks of gastric pain (Levine and Richter, 1935).

A cycle of approximately 40 days' duration associated with parathyroid deficiency has now been observed in a parathyroidectomized monkey, and a cycle of about the same length of time has been observed in a patient with a parathyroid deficiency.

Cyclic Behaviour in a Parathyroidectomized Monkey

The two pairs of parathyroid glands were removed from a male *Rhesus macaque* which for one month had been kept on a low-calcium diet. Tetany appeared in the hands and arms and the animal assumed peculiar postures,

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particularly of the hind legs. Blood calcium dropped to 7·0 mg. per 100 c.c. ; blood phosphorus increased to 8·6 mg. per 100 c.c. After one month and a half the monkey was given access to water and a 2·4 per cent. calcium solution in separate graduated inverted bottles of the same type as those used for rats. The intake from each bottle was measured daily. It was found that parathyroidectomy had produced a marked calcium lactate appetite in the monkey, just as it did in rats (Richter and Eckert, 1939). The animal ingested large amounts daily, as much as 140 c.c. per day, with the result that the blood calcium increased to a higher level (11·2 mg. per 100 c.c.) and the phosphorus decreased to 2·95 mg. per 100 c.c.

Of particular interest to us was the fact that the calcium lactate intake curve showed regular cycles of approximately 40 days' duration. Fig. 1,

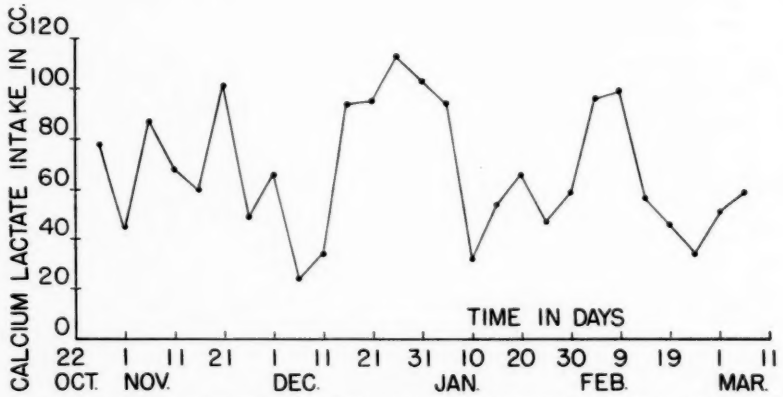

Fig. 1.—Chart of a parathyroidectomized monkey, showing cyclical variations in the daily intake of a 2·4 per cent. calcium lactate solution. The intake of tap water, to which the monkey was also given access, is not shown.

which gives the calcium lactate intake in 10-day averages over a period of 140 days, shows three very clear-cut and regular cycles. No observations were made on other phases of this animal's behaviour. Two other monkeys, parathyroidectomized at the same time, showed similar but less regular cycles.

Cyclic Behaviour in a Patient with Parathyroid Deficiency

The patient, a 56-year-old female school-teacher, came to the Phipps Clinic in May 1938 complaining of restlessness, depression, muscular cramps, and diarrhœa. Her illness had started 1 month previously, immediately after she had suffered a severe shock and had fallen unconscious as a result of the explosion of an ammonia tank and inhalation of the fumes. She began to sleep poorly, had no appetite, and could not concentrate ; she frequently had suicidal thoughts.

She gave a history of two previous depressions, one in 1924 which lasted only a few months and one in 1930 at the menopause which lasted about two years. At this time she received X-ray treatments for artificial induction of the menopause. After 1932 she had several depressive spells which lasted only a few weeks, at which time she appeared to benefit from sex hormone treatment.

After the patient had been in the clinic for more than 2 months, the symptoms of parathyroid deficiency which had been present to some degree during this time became prominent. Towards the end of her third month in the clinic, she showed a fine tremor of the hands, fibrillary twitchings of the arm muscles, and the Chvostek and Trousseau tests were positive. She had a low blood calcium (5·8 mg. per 100 c.c.) and a high blood phosphorus (as high as 8·7 mg. per 100 c.c.). On admission her vision was poor and later it became increasingly deficient, due to cataracts which formed in both eyes. X-rays showed a marked and uniform degree of decalcification of the bones.

At the end of the third month she was started on calcium therapy and at first given a variety of calcium compounds—calcium lactate, gluconate, and chloride. Later we attempted to repeat an observation made on rats and monkeys by leaving a 2 per cent. calcium lactate solution constantly within her reach with instructions to drink as much as she wanted. Almost from the beginning she drank approximately 1 litre, or 20 gm., of the calcium lactate per day ; however, contrary to our orders she limited the intake to that amount. Since the intake of the calcium lactate solution was not permitted to vary with changes in calcium appetite as it was in the animals, we could not determine whether it also showed cyclical variations. The patient also received 1 c.c. per day of A. T. 10* (Dihydrotachysterol) for several 4–5-day periods during the course of the calcium therapy.

We gave her calcium in the form of the lactate solution, since parathyroidectomized rats consistently showed a greater preference for calcium lactate and also thrived on it. Recently Wilson (1938) reported that calcium lactate when given in solution is more effective in parathyroid tetany than any of the other calcium compounds given either in solution or in crystalline form. Within 4 weeks the patient's blood calcium increased to 10·3 mg. per 100 c.c. and her phosphorus decreased to 5·6 mg. per 100 c.c. Her blood-clotting time returned to a more normal level and operations were performed for the removal of the cataracts. She was discharged in January showing a marked improvement in behaviour and a return to almost normal mood.

During the three-month period before the calcium therapy was started, the patient's behaviour showed two cycles of approximately 40 days' duration. After the calcium therapy was started, there was almost no tendency toward cyclical behaviour. Fig. 2 shows a part of the patient's behaviour chart. Markings characteristic of normal behaviour are shown at the top and markings characteristic of depressed behaviour are shown at the bottom. During her first 3 weeks after her admission, from 29th May to 20th June, the patient's behaviour was characterized by preoccupation, sadness, a slow and hesitant manner, irritability, indifference to ward activities, and unwillingness to

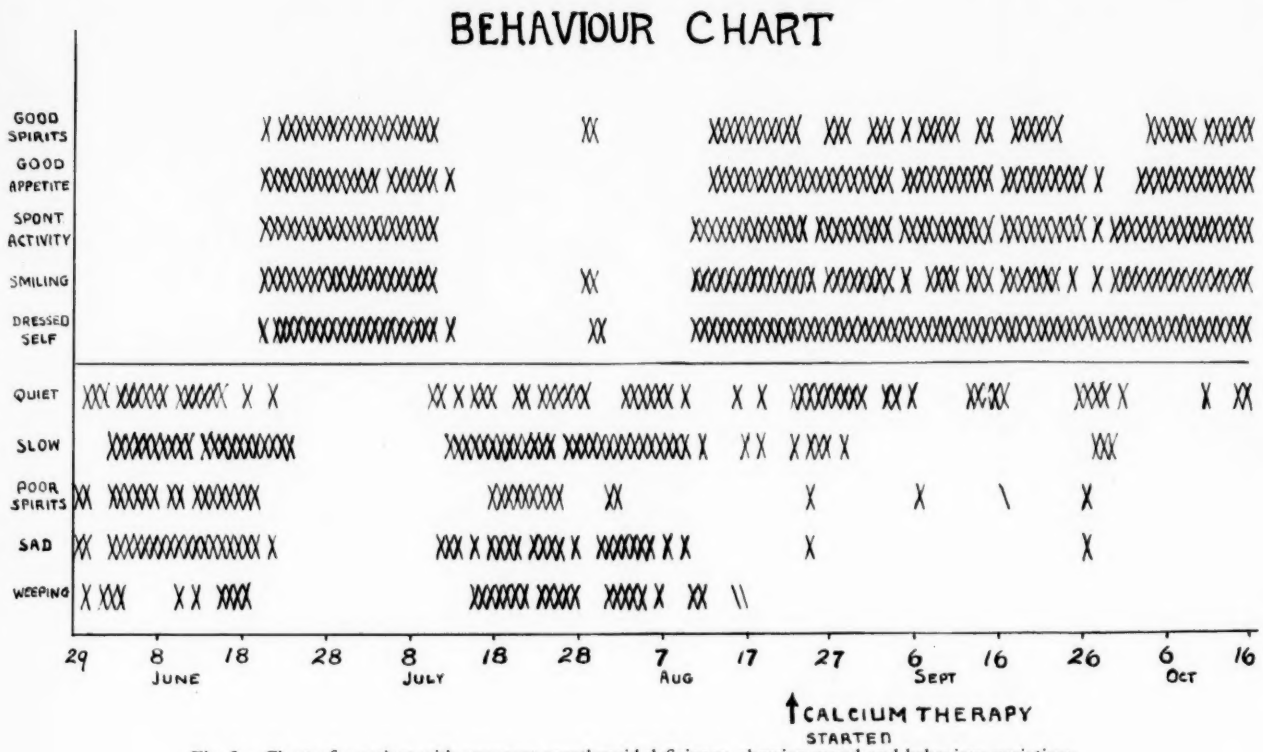

Fig. 2.— Chart of a patient with apparent parathyroid deficiency, showing mood and behaviour variations

co-operate. She was very quiet except for occasional evidences of bad temper ; she had only a fair appetite. She had to be dressed by the nurse because of her slowness and indifference. A few excerpts from the nurse's notes for 3rd June, 7 days after her admission, shows the character of the patient's behaviour during this phase :

" Patient got up, assisted by nurse, and walked slowly to bathroom as if in pain ; nurse had to help her dress ; she complained that her muscles felt so stiff. . . . She would stop and stare into space as if she didn't know what to do next. Walked up and down corridor looking at her feet, and grins foolishly. Seemed to lapse in memory at times. ' Sometimes I think I'm not anybody.' ' You must tell me what to do. I can't seem to think.' After supper did not enter into conversation or games with other patients. Said she would like to drown herself in the tub. Was in very low spirits, wore a frown on face all evening. Retired saying, ' I wish I would smother and not wake up.' "

Seventeen days later, on 20th June, there was an abrupt upswing, a remarkable change in behaviour, characterized by a pleasant humour and a good appetite ; the patient was smiling and co-operative, interested in ward activities, and was able to dress herself. The nurse's notes for this period describe her cheerfulness and normal behaviour :

" Up early, greeting others pleasantly ; needed little assistance in dressing. Seemed in good spirits, laughing and joking, and ate very well. Took an active part in games at gym. Walked about with much more pep. ' I never knew I could feel so low and then come up again.' "

After three weeks of this marked improvement, the patient relapsed and there was an immediate downswing, as can be seen on the behaviour chart, from 11th July to 10th August. The patient became moody, irritable, and unco-operative, with behaviour similar to that during her first 3 weeks. The nurse's notes are typical as for the first period.

This part of the cycle continued for about 4 weeks, when again there was a marked change for the better around 10th August. The patient showed normal behaviour, as can be seen on the chart, with only a few sporadic markings below. On 23rd August the patient was started on calcium therapy. At the end of 3 weeks, when the patient was expected to show a drop in mood according to the previous cycles, no change in behaviour was apparent. Her appetite was good and she showed fairly normal mood and behaviour, except for a slight lapse which occurred in September. This minor drop in mood and behaviour came about a week later than was expected, but was not marked in intensity, and the patient showed almost normal behaviour until her departure in January.

The basis for this illness was never determined. The ammonia explosion may have greatly exaggerated an already existent parathyroid deficiency, or the ammonia fumes may have actually produced the parathyroid deficiency.* MacCallum and Voegtlin (1909), in their experiments with calcium tetany in

* The medical aspects of this case will be discussed in detail in another paper by Dr. Howard and Dr. Emerson of the Endocrine Clinic of the Johns Hopkins Hospital.

parathyroidectomized animals, first mentioned the existence of an increased ammonia output in the urine and the increase in ammonia in the blood. Carlson and Jacobson (1911) substantiated these results, but were able to offer no proof of any ætiological relationship between the ammonia content of the blood and parathyroid tetanyl.

Discussion

The mechanism involved in the production of cycles by removal of the various endocrine glands still remains undetermined. From our experience with cyclic phenomena in rats we have concluded that the manifestation of any marked cyclic changes indicates a disturbance in some part of the endocrine system. In the well-functioning normal individual the various cycles existing in the different organs of the body become so perfectly fused that no cycle appears. However, disturbance in any one gland may release a cycle in another, and thus the pattern is upset and a new rhythm is established which shows itself in the behaviour as a phenomenon not ordinarily present. This dependence of the cyclical changes on the interrelationship of the various glands is brought out clearly in a recent paper by Horwitz and Harris (1936) on a psychosis associated with menstruation. Thyroid treatment not only caused the cycles to disappear but also brought about complete recovery from the psychotic symptoms.

McCullagh and Kearns (1935) have observed recurrent acute attacks of tetany in parathyroid deficient patients immediately preceding and during menstrual periods. For further evidence of the close relationship between tetany and the ovaries, they state that in 176 cases of tetany only nine were men; and that Boothby, Haines, and Pemberton (1931) found only one in 88 cases of tetany. They state also that recurrent attacks of tetany were never observed in women who had passed the menopause. The fact that our patient passed the menopause 2 years before her attacks started would indicate that they could not have depended on cyclic changes in the ovaries, unless we are to assume that such cycles persist postmenopausically. That the cyclic variations brought out by parathyroid disturbances have a duration of approximately 40 days in monkeys and in the human studied and only a 15–20-day duration in rats is not inconsistent with our knowledge of the difference in other organic cycles in these three species. Thus, in the rat the œstrous cycle had only a 4–5-day duration, while in monkeys and humans it averages 28 days. With more knowledge regarding the cycles in different species, it may be possible to determine some general underlying principle upon which the frequency of the cycles depends.

The fact that regular cycles of behaviour have been exhibited in rats and monkeys with disturbed glandular systems and, more particularly, the cycles mentioned above in parathyroidectomized animals would make it seem likely that the cyclical changes observed in this patient were definitely connected with the parathyroid deficiency. Moreover, this is in part substantiated by the fact

that with the calcium therapy there was almost complete disappearance of the cyclical variations and the abnormal mood changes. Also, the fact that this patient had passed the menopause may have contributed to the production of these cycles.

A suggestion of similar cyclic behaviour is also found in one of two cases of psychosis in tetany described by Knospe (1938). Following operation for exophthalmic goitre the patient developed parathyroid insufficiency and went through two phases with anxiety, hallucinations, and overactivity, each lasting about 4 weeks and separated by a more lucid interval of about 2 weeks during which she became amenable and gained insight.

It may be pointed out that in the animal suffering from parathyroidectomy the cycles were shown in an increased appetite for calcium ; in the patient these cycles occurred only when calcium was denied and cleared up on calcium therapy.

We believe that a search of the records of patients with parathyroid and other glandular disturbances may reveal similar cases evidencing cyclic behaviour.

Summary

Three parathyroidectomized monkeys kept on a low-calcium diet drank large amounts of a 2·4 per cent. calcium lactate solution, thereby alleviating their symptoms of insufficiency. Their intake of calcium lactate solution showed fairly regular cycles averaging 40 days in length.

A woman 56 years of age suffering from a parathyroid deficiency showed quite regular cyclic variations in mood and behaviour with a duration of approximately 40 days. For the first half of each cycle she was depressed and slow ; and for the second half she was fairly normal. After calcium therapy these cycles disappeared.

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HYPOGLYCÆMIC SHOCK AND THE GRASP-REFLEX

THE EFFECT OF INSULIN SHOCK ON BULBOCAPNINE CATALEPSY IN MONKEYS

BY

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(RECEIVED 10TH AUGUST, 1939)

IN a previous communication (Kennedy, 1939) an account has been given of the effects of cardiazol convulsions, such as are used in the treatment of clinical catatonic states, upon the catalepsy-like condition seen in bulbocapnine intoxication in monkeys. A study was made of the effects of convulsions on the grasp-reflex which is invariably present with this state in the bulbocapninized monkey, the intensity of the response being measured by the hanging-time method of Richter (1931). It was shown that the effect of the convulsions was to increase very considerably the cataleptic component of the state produced by bulbocapnine in much the same way as does the inhalation of a high concentration of carbon dioxide (Paterson and Richter, 1932), and that the period during which the grasp-reflex was present was greatly prolonged, though the convulsions alone produced only a transient hanging-response.

The purpose of the work to be described was to compare these effects of the induced convulsion with those of hypoglycæmic shock. The first object, therefore, was to reproduce in monkeys a condition as nearly as possible resembling therapeutic insulin shock and to determine its effect on motility and upon the grasp-reflex. Having thus standardized the effects of insulin on each animal used, it was then possible to investigate the effects of the hypoglycæmic state on the catalepsy and grasp-reflex phenomena produced by bulbocapnine.

Technique

The animals used for these experiments were six adults of the *Macacus Rhesus* species, each weighing about 3·5 kilos. The apparatus for measuring the duration of the hanging-response has been described in detail previously (Richter, 1931 ; Richter and Paterson, 1932), and consists of an horizontal brass bar, $\frac{3}{8}$ in. in diameter, held by two upright stands about 4 ft. above a net stretched over a frame, into which the animals fall when they cease to grip the bar. During the experiments trials of the

hanging-response were made every 10 minutes, and on each occasion both hands were tested separately, the one which was not being tried being tied down, with the feet, by means of a strip of muslin, in order to prevent the animal from using them to grip the bar. At each trial the monkey was held by the head, while the palm of its free hand was allowed to come into contact with the bar, when, if the response was present, grasping occurred and the animal was allowed to hang free. The time from releasing the animal and its falling into the net was taken with a stopwatch and recorded as the hanging-time. Before the experiments the six monkeys were tested on several occasions and it was found that the response was not present and that on being put to the bar they dropped at once and attempted to escape.

In previous experiments with the grasp-reflex (Richter and Paterson, 1932) the insulin was given intravenously, but it was found that its effects were far less constant and uniform than by the subcutaneous route, and this was employed in the present series. Preliminary experiments were made in order to find a dosage which would produce a state as nearly as possible resembling therapeutic hypoglycæmic shock as seen clinically, and it was found that under carefully controlled conditions a dosage of one unit per kilo produced the most uniform results. It was found that these results could be obtained only if the animals had been starved for 24 hours and if elaborate precautions were taken to preclude access to small quantities of carbohydrate, such as might be obtained by chewing the sawdust in the cages. It was also found necessary to reduce their activity to a minimum by reducing the amount of light and extraneous noises. To this end the six monkeys were kept in a row of cages in the same room as the apparatus for 24 hours before the experiments, so that they were not unduly stimulated and could be taken out one by one with a minimum of struggling, examined, and at once put back. The experiments were carried out at weekly intervals, the weight and activity of the animals being recorded in the interval.

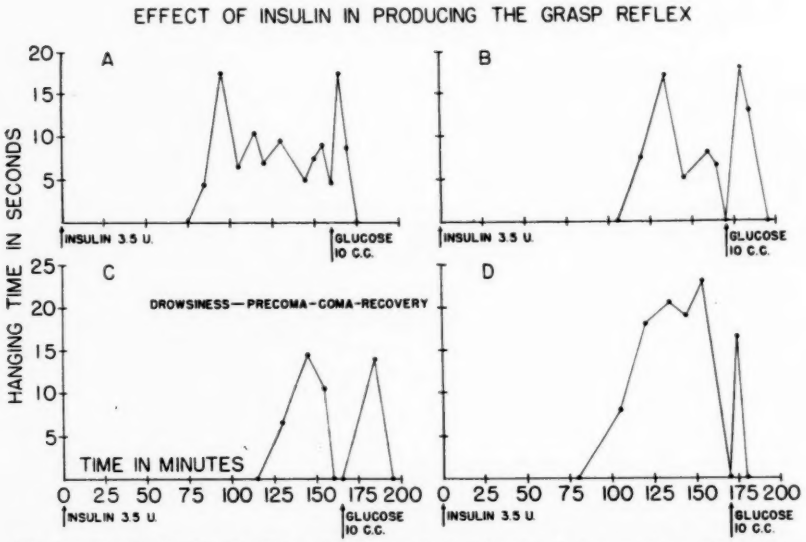

Fig. 1.—*Graphs showing the effects of insulin on the hanging-time in four monkeys.* The reflex appears 80–110 minutes after the administration of insulin and continues until the onset of coma. On interruption of the coma with glucose given by stomach-tube the reflex appears again briefly during recovery. The times given are the average hanging-times from the two hands.

After the insulin had been given, the activities, appearance, and results of examinations of the animals, as well as the hanging-times, were recorded in relation to the times at which they occurred. With the times after injection as abscissæ and the hanging-times as ordinates, graphs were made (Fig. 1) to illustrate the changes in the hanging-response. When the hypoglycæmic shock had progressed to the stage of deep coma, it was interrupted by giving 10 c.c. of a 50 per cent. solution of glucose by means of a stomach tube, which offered no difficulties in the unconscious animal. The bulbocapnine was injected subcutaneously as a 10 per cent. solution, and a dosage of 15 mg./Kilo was used as this gave the most uniform results.

Procedure

In the first part of the experiment the behaviour and reflex changes, including the hanging-response, were studied after the subcutaneous injection of insulin. In the second part the object was to study the effects of hypoglycæmic shock on the behaviour, cataleptoid phenomena, akinesia, tremors, and grasp-reflex changes produced by bulbocapnine, and for this purpose the effect of bulbocapnine alone was first determined and hanging-curves obtained, and then the drug was injected at different periods during the action of insulin, a week elapsing between each experiment. Thus from each animal a record and curve was obtained of the action of insulin alone, of the action of bulbocapnine alone, of the effect of giving both simultaneously, of the effect of giving bulbocapnine just as the pre-comatose stage was commencing, and of the effect of giving it at the time that the coma was interrupted by giving glucose. It was thus possible to compare the effects by a parallel series of observations.

Results

Effect of Insulin on the Normal Monkey

The following account is based on the observations common to the records of all of the six animals used. No effect was noted for about 50 minutes after the injection, the animals sitting quietly in their cages. At the end of this period some restlessness appeared, and they would begin to scratch the floor of the cage in search of scraps of sawdust which they would put in their mouths and chew, or they would reach into the next cage to explore their neighbour's back for food. This activity was intermittent and would be succeeded by periods in which their heads would nod and eyelids droop and they would blink frequently. From this drowsiness they could at first be readily aroused by handling or by making a noise or exhibiting food, but the active periods soon became shorter, and at the end of 70 minutes their heads were bowed down and their eyes closed for most of the time. Even when very drowsy, however, the animals would frequently lick their lips and put their hands to their mouths as if hungry. At this stage the muscles had become hypotonic and the tendon reflexes were rather more brisk than normal.

Between 80 and 100 minutes after the injection, the hanging-response appeared when the hand was allowed to grasp the bar, thus stretching the flexor tendons of the forearm, but no grasping was elicited by stroking the palm lightly with a brush. The mean hanging-times for the two hands at different periods after the injection of insulin for four of the animals are shown in Fig. 1.

In this figure the period of the hypoglycæmia has been divided arbitrarily into four stages of drowsiness, pre-coma, and recovery, the pre-coma stage commencing with the appearance of the hanging-response.

Shortly after the hanging-response had appeared, the animals once more showed short periods of excitement in which, without otherwise moving very much, they glanced rapidly from side to side and at the same time showed muscular irritability and increased tendon reflexes. The glancing movements then lost their apparently purposeful character and almost imperceptibly developed into a marked spontaneous nystagmus which later, in some of the animals, was of the scintillating type. This stage was reached some twenty minutes after the appearance of the hanging-response.

With the nystagmus, twitching and sudden movements of the limbs began to appear at intervals of 3 to 5 minutes, and in the intervals muscular hypotonia became very profound, though the tendon reflexes were very brisk and individual muscles would contract on being lightly tapped. Soon these periods of muscular irritability became more intense and somewhat more frequent, occurring at intervals of 2 to 3 minutes. The movements gradually became more widespread and assumed the character of convulsions. If the monkeys were handled at the time when such a convulsion was expected, the stimulation attendant on handling would bring it on. When this stage of intermittent convulsions had been reached, the animals showed no appreciation of visual or auditory stimuli and were evidently unconscious. Immediately after each bout of convulsions the muscular hypotonia was extreme. In two animals short periods of clonic movements occurred, of about 5 seconds' duration. At 160–170 minutes after the injection a rapid change came over all the animals. The muscles became toneless, cyanosis and frothing at the mouth appeared, together with drenching perspiration and a rapid collapse in which the tendon reflexes and the hanging-response disappeared. This stage of deep coma came on in the course of less than 5 minutes and necessitated the giving of glucose. This was given by means of a stomach-tube and syringe, and within a minute consciousness returned and the animals began to look about. The hanging-response also reappeared transiently during this stage of recovery, to disappear again as behaviour became normal. After the experiment the animals did not seem very exhausted and had voracious appetites. At no phase of the action of insulin were any cataleptic phenomena observed.

Effect of Hypoglycæmia on Bulbocapnine Catalepsy

Effect of Bulbocapnine alone.—The effects of bulbocapnine in the monkey have been previously described (Kennedy, 1939) and will not be given in detail. Shortly after the injection, the hanging-response appeared, accompanied by the akinesia, tremors, and salivation. No marked catalepsy was observed, but there was a slight tendency to maintain impressed postures about 40 minutes after the injections. The duration of the hanging-response was recorded graphically as before (Fig. 2, A). For simplicity the average hanging-time for the two hands is given, there being usually no great difference between them.

Effect of Bulbocapnine and Insulin : when given simultaneously.—For the first 40 minutes the effects observed resembled those brought about by bulbocapnine alone, except that at the first trials the hanging-response was in all the animals appreciably longer (Fig. 2, C). As the effects of the bulbocapnine

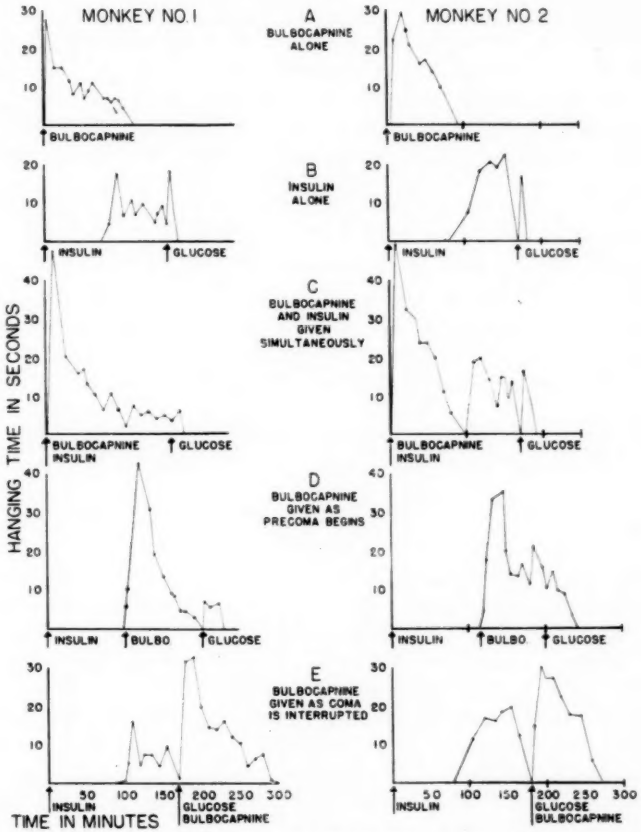

Fig. 2.—*Graphs from two animals showing the effects of the administration of insulin and bulbocapnine in different time relations on the hanging-response.* The vertical arrangement enables the summation of the effects to be appreciated.

began to wear off, the tremors disappeared and the hanging-times became shorter, the animals began to blink and to nod as the effect of the insulin became evident. The hanging-times then increased again and the nystagmus, muscular irritability, and convulsive movements appeared in the same time-relations as when insulin was given alone, and were followed by the stage of deep coma and collapse. Upon interruption the grasp-reflex reappeared or increased almost exactly as before. In respect of the hanging-response, apart from the high level at the commencement, the curves obtained may be regarded

as summations of those obtained with bulbocapnine and insulin separately (Fig. 2, A and B).

When Bulbocapnine was given as the Hanging-Response appeared.—In these experiments the effects of the insulin were observed up to the time of the appearance of the hanging-response and found to have very similar time-relations to those recorded 2 weeks previously. As soon as the grasp-reflex became evident, bulbocapnine was injected and at once the hanging-time increased to a level higher than obtained when either drug was given separately. At the same time a number of new phenomena were observed.

The animals were very still and the tremor which might have been expected at this time from the bulbocapnine was notably absent in four and only slightly present in two of the animals, in both of which it later disappeared.

In the table (Fig. 3) it is seen that a considerable tremor-free period was

NO. OF ANIMAL	TREMOR			CATALEPSY	GRASPING	
	MINUTES AFTER ONSET OF BULBOCAPNINE EFFECT				SPONTANEOUS	ON STIMULATION OF PALM
	15	30	45			
I	X	—	—	—	X	X
II	X	—	—	—	X	X
III	—	X	X	XX	—	X
IV	—	—	X	—	X	X
V	—	—	X	X	X	X
VI	—	—	—	X	X	X

Fig. 3.—*Table showing differences in the phenomena observed in the six monkeys in the period following the injection of bulbocapnine during insulin pre-coma (see also Fig. 2, D).* In all the animals there was an inhibition of the tremors for at least 10 minutes of the period during which it was present with bulbocapnine alone.

present in all the animals at a time when, had they been under the influence of bulbocapnine alone, tremors would have been well marked. In three animals slight catalepsy was present, but they would not maintain impressed postures against gravity to any extent. When the hands were put to the bar, grasping occurred very readily in all and within 15 minutes of the injection of bulbocapnine, in five of the six animals the hands and forearms spontaneously took up a flexed position and grasping occurred without any local stimulus. In all, grasping occurred at this period when the skin of the palm was lightly touched with a brush. The spontaneous grasping was accompanied by a flexed position of the arms, extreme muscular irritability, and drawing up of the knees and forward bending of the trunk. This condition persisted for 20–30 minutes, during the latter part of which time nystagmus developed and was followed by intermittent convulsive movements which increased in frequency and magnitude until the stage of sweating, cyanosis, and collapse with gross hypotonia supervened and necessitated the giving of glucose. In three animals in which there had been no tremor at first, this appeared as the hanging-time, which had

been greatly prolonged, abruptly became shorter. A summary of the signs evident during this period in the different animals is shown in the table (Fig. 3).

When Bulbocapnine is given as the Hypoglycæmia is interrupted.—The same effects were noted after the injection of insulin as before, and it was observed that the time-relations of the changes and the contour of the hanging curves were roughly the same for each animal on each occasion. After the stage of deep coma, bulbocapnine was given at the same time as the glucose, and it was observed that when the hanging-response appeared, the hanging-times were at first a little longer than when bulbocapnine alone was given. Apart from this there was little difference, the descriptive data and hanging-curves being very similar (Fig. 2, E).

Discussion

From the experiments described it is evident that when insulin is given to monkeys that have been previously starved and kept so that external stimulation is reduced to a minimum, the phenomena observed are closely comparable to those seen in man during hypoglycæmic shock treatment. It is seen that a constant accompaniment of the pre-coma stage in the monkey is the appearance of the hanging-response which disappears with the onset of gross hypotonia and collapse and reappears briefly in the stage of recovery after glucose has been given.

Although, after the action of insulin alone, there was a period during which the animals became drowsy and akinetic, no severe catalepsy was observed such as has been described in cats (de Jong, 1931) and in mice (Divrey and Evrard, 1937). The hanging-response, therefore, was not associated with catalepsy as it is in the monkey after bulbocapnine (Richter, 1931) or bulbocapnine-cardiazol (Kennedy, 1939).

The convulsions seen in monkeys during insulin hypoglycæmia differ in a number of ways from those induced by intravenous injections of cardiazol. They are multiple and intermittent, have a good deal of prodromal twitching, and tend to be precipitated by peripheral stimulation. There is no usual pattern such as is seen in the cardiazol convulsion, and there is no sharp distinction between minor twitches and convulsive movements, all intermediate stages being present. Clonic movements were seen in two of the animals, but they did not occur with every convulsion and were very brief in duration. As seen in these experiments, the seizures could not be described as epileptiform and their occurrence seemed to result from an intermittent exaltation of neuromuscular irritability rather than from a process of spreading cerebral excitation. The occurrence of increased neuromuscular excitability in association with drowsiness and akinesia and with the appearance of the grasp-reflex would suggest that, unlike the cardiazol convulsion, the insulin convulsion is of the nature of a release phenomenon.

The reappearance of the neonatal grasp-reflex in the adult monkey would not appear to be a phenomenon indicative of a single type of dysfunction in the

central nervous system, but rather the common physical sign of a number of abnormal processes in the upper neurons. It appears, together with the drowsiness resulting from the action of some sedatives (Richter and Paterson, 1932) and during the action of a number of substances which have in common the property of producing transient remissions in some catatonic states, and, as already mentioned, it is always present in association with the catalepsy produced by bulbocapnine (Richter, 1931). It has been suggested (Kennedy, 1939) that it is also a part of the extrapyramidal syndrome produced by that drug. It has been further suggested that when it appears as the result of more than one train of causation, the hanging-time is longer than when a single cause is operative. This view receives confirmation in the present experiments where it can be seen that when bulbocapnine and insulin are given to the same animal, either simultaneously or in sequence, the results, so far as the hanging-response is concerned, represent a simple summation of the action of the two agents, as is well seen in the series of curves in Fig. 2. There are, however, two periods during which there is a greater prolongation of the hanging-time than would be expected on this basis. The first of these occurs when the insulin and bulbocapnine are given simultaneously (Fig. 2, C). Here the prolongation of the hanging-time is brief but constant, and it is presumably due to the absorption into veins of a quantity of insulin sufficient to increase the hanging produced by bulbocapnine, though when the insulin is given alone it is insufficient to cause hanging by itself.

The second occasion when the hanging-time may be rather longer than would be expected from simple summation occurs when the bulbocapnine is given at the time the insulin is approaching the height of its effect, in the pre-coma stage, and it is this period which is the greatest theoretical interest. As has been seen, for a period of about 30 minutes phenomena are present which are not brought about by either drug alone, and there is a disappearance of a conspicuous component of the bulbocapnine picture, namely the tremor. During this period, spontaneous grasping occurs and the animal takes up a position with the forearms flexed. This position, with the attendant muscular irritability, is not unlike that seen in tetany. That the presence of tetany as a complicating factor is not to be excluded lightly is indicated by the fact that bulbocapnine causes a considerable fall in the blood calcium of cats (Katzenelbogen and Meehan, 1933), and it is probable that the tendency to tetany is increased by the strong alkalizing action of the insulin. During this critical period a grasp-reflex was obtainable from all the animals by lightly stroking the palm. While this might be taken to indicate the presence of a different type of grasp-reflex initiated by a skin-sensory stimulus, in view of the observation (Bieber and Fulton, 1938) that in the " pre-motor monkey " the grasp reflex can be obtained by lightly touching the palm, even when the cutaneous nerves have been blocked with a local anæsthetic, it seems possible that it may be activated by stimulation of the flexor tendons, just as is the reflex that gives rise to the hanging-response. It is likely, however, that even if a sensorimotor grasp-reflex of the type described by Walshe and Robertson (1933) does not appear, the ease with which grasping is obtained indicates a further process of release.

The presence of spontaneous grasping and of an associated attitude of the forearms is also suggestive of further cortical release, since the grasp-reflex is to be regarded as part of a less localized response, whether this be of the nature of a forced grasping movement (Walshe and Robertson, 1933) or of a postural reflex (Bieber and Fulton, 1938), more of which is revealed when the action of insulin is added to that of bulbocapnine.

In the table (Fig. 3) it can be seen that at this critical period in the pre-coma stage, in all the animals the tremors are absent for at least 10 minutes at a time when, under the influence of bulbocapnine alone, they would be unmistakably present. In view of the observation (Schaltenbrand, 1925; Ferraro and Barrera, 1932) that tremor does not occur on the contralateral side in a bulbocapninized, hemi-decorticate animal, it would seem that the absence of tremor might be explained by a temporary suspension of cortical activity, comparable to that which presumably causes the cessation of extrapyramidal tremors in sleep. This again would suggest that the action of insulin is a depressant one predominantly at the cortical level.

Summary

1. Hypoglycæmic shock was induced in six monkeys. The phenomena observed are essentially similar to those seen in therapeutic hypoglycæmia in man.

2. The hypoglycæmia was accompanied by a reappearance of the neonatal grasp-reflex, which disappeared when coma became deep and reappeared briefly during the phase of recovery.

3. When bulbocapnine is given at different periods during the action of insulin, the general effects and those in regard to the hanging-response are a summation of the individual effects of the two drugs, except when the peak of action of both drugs coincides, when new phenomena appear.

4. These consist of disappearance of the tremors caused by the bulbocapnine and the appearance of spontaneous grasping, together with a grasp-reflex obtainable on light stimulation of the palm.

5. Hypoglycæmic shock has no effect on the cataleptic manifestations induced by bulbocapnine, nor does it itself produce catalepsy in the monkey.

6. Theoretical reasons are adduced from the experiments for the supposition that the action of insulin is predominantly a depressant one on the cerebral cortex.

I am indebted to Dr. Curt P. Richter, in whose laboratory at the Johns Hopkins Hospital, Baltimore, U.S.A., these experiments were performed, for valuable advice and assistance. The work was carried out during tenure of a Rockefeller Neuropsychiatric Fellowship.

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DEGENERATION OF THE PAPILLO-MACULAR BUNDLE IN APES AND ITS SIGNIFICANCE IN HUMAN NEURO-PATHOLOGY

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Introduction

ROTHMANN (1906), Schröder (1908), and Schob (1931), published the early work on spontaneous lesions of the peripheral optic pathways in isolated cases of apes who died of a diffuse degenerative process in the white matter of the centrum ovale and (or) the spinal cord. These authors gave contradictory descriptions of the lesions in the optic pathways. Scherer (1932), who first recognized the pathological identity of this spontaneous disease in apes with that known in the human as " sub-acute combined degeneration " (Scherer, 1937) described these optic lesions in more detail. He emphasized their comparative frequency in this condition, and compared them to the rare optic nerve degenerations reported in human subacute combined degeneration. During recent systematic researches on the peripheral optic pathways in monkeys dying from a variety of causes, degenerative lesions in the optic nerves, chiasma, and tracts were found in a surprisingly high percentage of the animals, without degenerative changes elsewhere in the nervous system. Also, in these animals, the keepers had not noticed any visual disturbance during life.

The purpose of this paper is first to describe the frequency, exact localization, and histological characteristics of these lesions, and to discuss the possible pathogenesis. Secondly, to compare these lesions with corresponding changes occurring in man and also with those in monkeys affected by definite degenerative changes in other parts of the nervous system (subacute combined degeneration).

Material and Methods

For the purpose of this work post-mortem examinations have been made on 27 apes, the majority of which were cercopithecidæ (*Macacus Rhesus*, different types of cercopithecus, cercocebus, etc.). In all cases, both optic tracts and the chiasma were examined by means of coronal sections which cut the nerve fibres in a somewhat longitudinal direction. In 13 of the cases the

intra-orbital portions of both optic nerves were examined by longitudinal and cross section. Frozen sections were stained with Scharlach Red for fatty degenerative products, by the Spielmeyer method for myelin sheaths, and with Cresyl Violet. In those stained for myelin, the commencement of the lesion was often difficult to detect, but the Scharlach Red and Nissl preparations showed even very slight changes. In the myelin stained preparations, artefacts may easily simulate degenerative changes, therefore only those preparations in which degeneration was confirmed by the Scharlach Red and Nissl stains, are quoted. Besides these 27 cases, 5 cases of pure optic degeneration, and the optic lesions in 15 apes with encephalo-myelosis, all observed before we began this research, have been carefully re-studied.

Results

Systematic Study.—In 19 of the 27 cases in which the peripheral optic pathways were examined no lesion was found. The remaining 8 had definite changes, always symmetrical, either in the optic tracts alone, or in the whole peripheral optic system. In none of these 27 cases could we find other degenerative changes in the white matter of either the central or peripheral nervous system. The optic lesions in these cases had never a focal, but always a fascicular and symmetrical character. However, there were definite differences from case to case in the intensity and extent of the degenerative lesions. These differences and the character of the lesions were as follows :

The initial lesion occurred in the upper postero-lateral field of the optic tract, and extended down from there to the central, and forwards to the under medial parts (Fig. 1). The lesion was always confined to a sharply limited bundle of

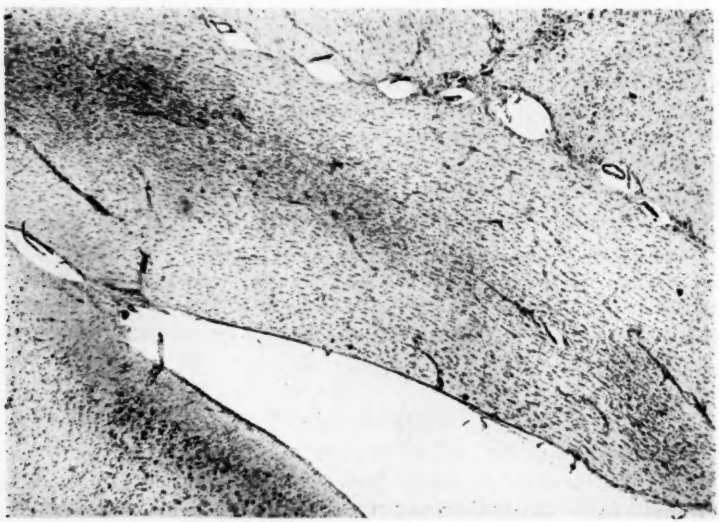

Fig. 1.—Optic tract, coronal section, Nissl stain. The degenerated field, recognizable by the multiplication of glial nuclei, goes from the upper lateral parts (upper left corner) to the lower medial parts of the tract (lower right corner). Same case as Fig. 2.

fibres. In the anterior half of the chiasma (Fig. 2) cross sections generally showed an extensive degeneration of the central parts, while a small portion of the fibres at the dorsal and ventral edge remained intact. The posterior half of the chiasma showed no degeneration.

At this stage the myelin stain showed no lesion, but with fat stains there was

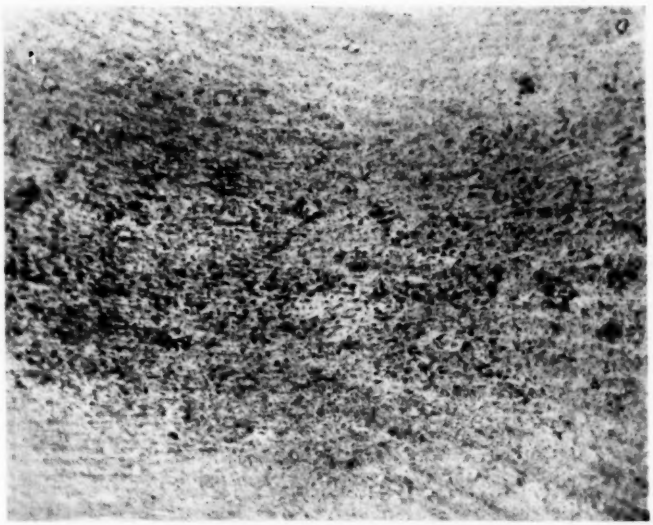

Fig. 2.—Anterior half of chiasma, coronal section, Scharlach red stain. The fat substances (black in the picture) are situated in a central location.

a definite fatty degeneration, and with nuclear stains a fairly pronounced multiplication of the glial nuclei (Fig. 1), limited exactly to the same field as the Scharlach Red coloured substances. These substances were evenly distributed in fixed glial elements (Fig. 5), and there were no compound granular cells. The intraorbital portion of the optic nerves in only one such case failed to show any lesion.

At the next stage, the lesion in the optic tracts showed exactly the same localization and extent, but the fatty degeneration had become more intense, and there was a commencing alteration in the myelin picture. However, the degeneration conserved the "fixed" type, and compound granular cells remained rare. In these cases, however, the intraorbital optic nerves showed definite lesions, and always in the same location. Cross sections of the optic nerve immediately behind the eye bulb showed a rather triangular field of degeneration whose apex coincided with the central vessels, and whose base was formed by the lateral surface of the nerve (Fig. 3, *a*). Posteriorly, where the central vessels had left their central position and approached the periphery, the degeneration covered a superficial field of semilunar shape, whose convex side coincided with the lateral surface of the nerve, while the concave side had a tendency to retract itself away from the central vessels (Fig. 3, *b*, 4). More

posteriorly, where the central vessels had left the nerve, the field had a rounder shape and retracted itself more and more from the surface (Fig. 3, *c*), becoming central in position in the most posterior part of the intraorbital segment of the nerve.

The limitation of the degenerated field was always sharply outlined and there was no doubt about the definite fascicular character of this degeneration

Fig. 3.—Cross-sections through the anterior (*a*) mid- (*b*) and posterior (*c*) parts of the intraorbital portion of the optic nerve. Spielmeyer stain for myelin. (*a*) and (*c*) same low magnification (*b*) higher magnification.

both in transverse and longitudinal sections. The histological character of the lesions was the same as described above for the optic tracts : first, a slight fatty degeneration with the appearance of the fat substance in the fixed glial elements and in mesenchymal cells of the connective tissue of the nerve (Fig. 4) and a

definite increase of glial nuclei in Nissl pictures. Second, a clear loss of myelin appeared in the same localization, while, with the intensification of the disintegration compound granular cells appeared, these generally not being very numerous. However, even in these advanced cases, the demyelinization of the affected areas was never complete, a considerable number of the myelin fibres always remained intact (Fig. 3, *b*).

Finally, and only in rare cases, a more diffuse degeneration was observed in

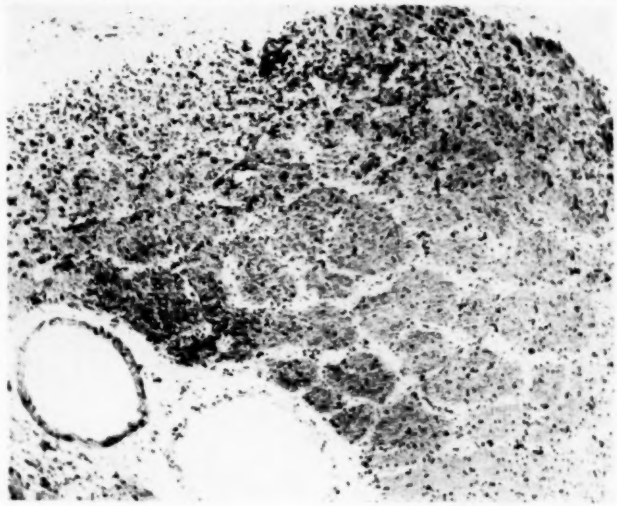

Fig. 4.—Cross-section through the intraorbital portion of optic nerve immediately before central vessels leave the nerve ; Scharlach red stain. Degeneration limited to the characteristic peripheral field (same case as Fig. 5).

the optic tracts and chiasma, covering practically the whole cross section of these structures, and no longer confined to the circumscribed bundle described above. But in one of these cases, in the intraorbital part of the optic nerves, a definite fascicular degeneration of a circumscribed fibre bundle was observed, whose location corresponded exactly to that of the optic nerve lesions in early cases. The character of the degeneration remained the same as in earlier stages, even in the optic tracts : fat globules, usually in the fixed glial elements, the arrangement of which was quite regular and followed uniformly the direction of the fibres (Fig. 5).

Isolated Optic Degeneration observed outside this Study.—The collections in our laboratory contained 5 other cases of monkeys, 2 of which have been published later in detail by Dr. Van Bogaert, with identical optic degenerations but without other white matter lesions. These had been observed before beginning our systematic researches. In 2 of these cases there were clinical symptoms of cecity, and the lesions were especially pronounced. In 1 case, the optic tract lesion was so severe that there was

already a zone of real softening. Unfortunately, only tracts and chiasma had been examined in all these cases, but in three cases at least, the localization and character of the optic tract lesions were the same as in the cases described above.

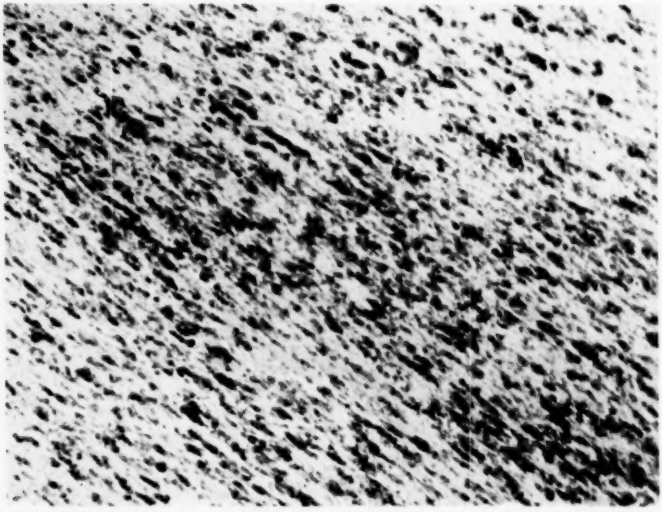

Fig. 5.—Coronal section through the optic tract of the same case as Fig. 6, Scharlach red stain. The optic tract shows diffuse degeneration. Degeneration products evenly distributed in fixed glial elements following the fibre direction. Compare with Fig. 8.

Character of Optic Degeneration in Cases of Encephalo-Myelosis.—The optic nerve lesions in apes with encephalo-myelosis (subacute combined degeneration) were re-examined after this systematic study. These lesions were described (Scherer, 1932) as a systemic degeneration of a fibre bundle in the upper postero-lateral part of the optic tracts (Fig. 6). This location corresponded exactly to that of the optic lesions described in this paper. As, in one of these cases, multiple focal lesions were seen in the anterior part of the optic tract, and as the anterior parts of the optic nerves from the other cases were not available, this fibre bundle lesion was considered to be probably a secondary degeneration caused by focal lesions elsewhere. These lesions on being re-studied, were without doubt due to a primary systemic degeneration of the bundle concerned, which might, in rare cases, be accompanied by focal lesions in the peripheral optic system, identical to the patches found in the spinal cord or centrum ovale. This conviction was based on evidence that in cases of encephalo-myelosis there occurred an undoubted degeneration of the same bundle, and also in the intraorbital part of the optic nerve, but unaccompanied by focal lesions in this part.

Fig. 7 shows the optic tracts and chiasma of such a case : the centrum ovale had the typical lesions of encephalosis, the intraorbital part of the nerve showed a typical, but quite advanced degeneration of the same bundle, without any

focal lesion. In the chiasma and optic tract a large fascicular zone of demyelinization was seen ; at the same time, a considerable number of newer and older patches of demyelinization were seen, some of which were confluent with

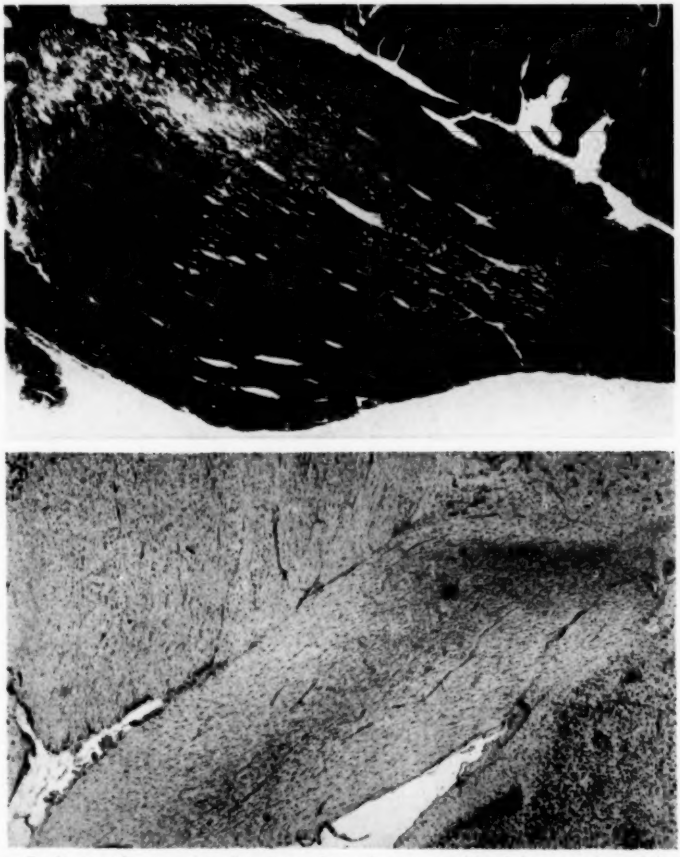

Fig. 6.—Optic tract from a case of commencing subacute combined degeneration of the spinal cord. (*a*) Most posterior part of the tract, myelin stain : degeneration of the lateral upper corner ; (*b*) More anterior part of the tract, Nissl stain : the degenerated field goes down from the upper lateral corner to the under medial parts. Compare with Fig. 1.

the degenerated fascicles. Fat stains showed the definite focal character of the disintegration (Fig. 8), and there was a predominance of " mobile " disintegration with numerous compound granular cells in these patches.

General Disease in Affected Cases.—From the 13 cases of isolated optic degeneration, 4 died from generalized tuberculosis, 2 from mild chronic lymphocytic meningitis, 3 from a general cachexia after clinical gastro-intestinal disturbances but without definite pathological lesions. In the

others the cause of death was not evident. Amongst the cases of encephalo-myelosis with optic degeneration, there were 3 with definite

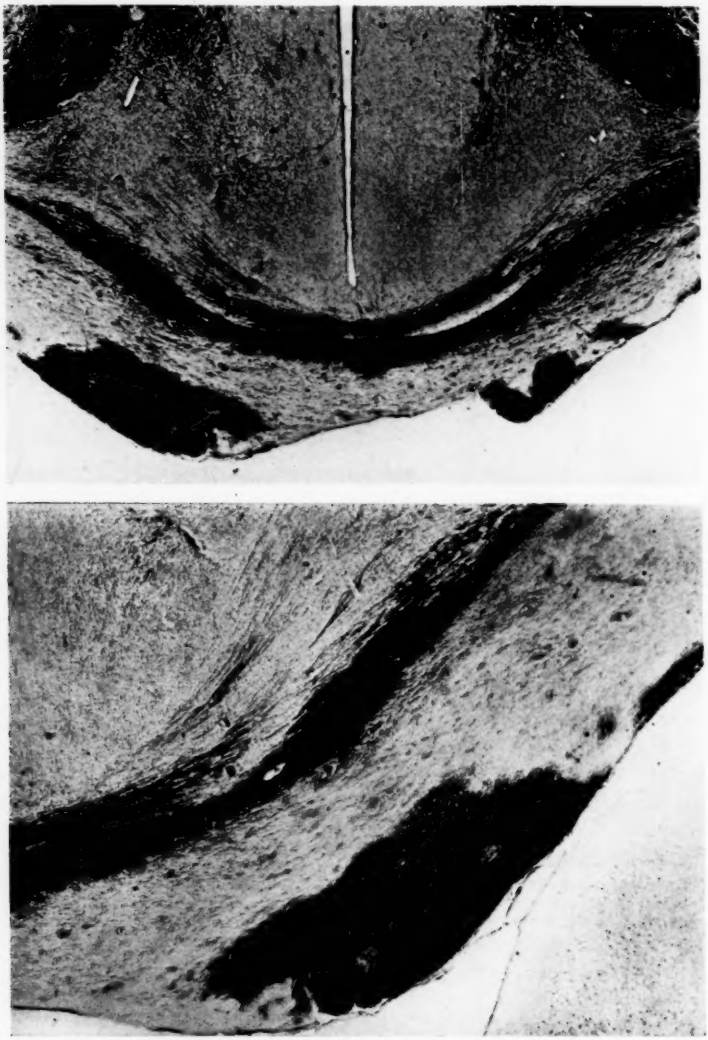

Fig. 7.—Systemic bundle degeneration and multiple focal lesions in chiasma and optic tracts of a case of encephalosis (cerebral form of subacute combined degeneration) Spielmeyer's stain. (*a*) General view, (*b*) detailed picture.

chronic colitis, 1 with generalized tuberculosis. Several of our old cases, and cases from the literature showed the occurrence of gastro-intestinal troubles. There was, however, no constant correlation : controls of the

optic pathways in numerous monkeys who died from generalized tuberculosis and severe chronic colitis showed that in spite of these conditions the optic pathways might be perfectly normal. But, although the gastro-intestinal tract

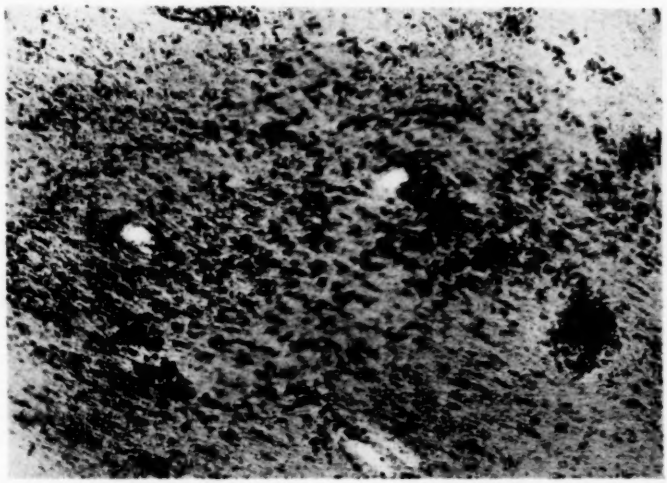

Fig. 8.—Scharlach red detail picture from one of the chiasma patches of Fig. 7. Note the focal character of lesions, the concentration of granular compound bodies around the vessels. Compare with Fig. 5.

in our earlier cases had not been examined carefully enough, there seemed to be an astonishing frequency of primary, or secondary (in generalized tuberculosis) gastro-intestinal troubles in cases of subacute combined degeneration as well as isolated lesions of the papillo-macular bundle.

Comment

We may say, therefore, that isolated symmetrical bundle degenerations in the optic nerves and tracts are frequent in captive monkeys which show no other lesions of the nervous parenchyma. In most cases they are so recent that a definite myelin loss is not readily recognized, but only a commencing fatty degeneration strictly confined to a definite fibre bundle. In other words, this seems to occur, in most cases, only a few days before death. The causes of death were, generalized tuberculosis, slight lymphocytic meningitis, and gastro-intestinal disturbances ; sometimes the necropsy revealed no clear cause of death. The degeneration seems to begin in the optic tract and to involve the optic nerves later. The lesions in the former are frequently more intense than those in the latter, and in one case with a very recent lesion in the tracts, the intraorbital part of the optic nerves did not show any lesion at all. However, this point still needs further study. The first question to ask is, what kind of fibres show this pronounced vulnerability ? and the second, what is the ætiology of this curious process ?

The constancy of location presented by this lesion in all positive cases, as well as in different parts of the peripheral optic pathways, seems to suggest that it is due to degeneration of a definite fibre unit. The location of this fibre unit corresponds to that of the papillo-macular bundle in man, as given in the schema of Uthoff-Abelsdorff. Furthermore, the finer histological characters (scarcity of compound granular cells, incomplete demyelinization, etc.), are the same as described in papillo-macular bundle degeneration in the human (see Abelsdorff, 1928). There is present, therefore, in all these monkeys, a systemic degeneration of the papillo-macular bundle, and it is only in very advanced cases that the degeneration affects the whole of the optic tracts. With regard to the cases where this bundle degeneration is part of subacute combined degeneration in monkeys, we wish to draw attention to the fact that optic atrophy in human subacute combined degeneration has been observed by Bielschowsky (1901), Ungley and Suzman (1929), Ossenkopp (1931), Courville and Nielsen (1938), Rothfeld (1938), and others. Unfortunately careful study of such optic lesions in man are still lacking.

The problem of the ætiology is more difficult to answer. It is certain that the affected animals died from quite different diseases and all of which certainly had a much longer duration than the degeneration of the papillo-macular bundle. As this degeneration seems to be frequently a terminal complication the possibility of an alimentary deficiency has to be considered as a cause.

Let us consider here (*a*) the degeneration of the papillo-macular bundle in man, and (*b*) the degeneration in the same bundle in apes with lesions of the white matter of the type of " subacute combined degeneration " (encephalomyelosis).

(*a*) The sole fact recognized in the human papillo-macular degeneration (" neuritis retrobulbaris "), is that its ætiology may differ greatly. The most frequent causes seem to be poisoning by alcohol, or nicotine, and the diseases diabetes mellitus, hyperemesis gravidarum, etc., that is to say the same conditions that frequently cause peripheral nerve degeneration. These peripheral " neuritides " are actually considered to be due to secondary B avitiminosis following on the primary intoxication or metabolic disorder. Cases of retrobulbar neuritis have also been observed (quoted after Schieck, 1938) in pellagra, beri-beri, carcinomatous cachexia and by generally insufficient nutrition (Moore, 1934). The hypothesis that a mechanism similar to that acting in peripheral neuritis may be responsible also for the degeneration of the papillo-macular bundle needs careful consideration, and has been discussed recently in some ophthalmological papers (Yudkin, 1933 ; Carroll, 1937 ; Paternostro, 1938 ; and others) but without definite conclusion.

(*b*) The fact that an identical degeneration of the papillo-macular bundle is one of the most constant features to be observed in subacute combined degeneration in monkeys (in the spinal as well as the cerebral forms) speaks again in favour of an avitaminosis or at least a deficiency as the origin of this bundle degeneration when it occurs as an isolated lesion. Since my first publication about subacute combined degeneration in monkeys, I have emphasized the possibility of its being due to an avitaminosis. All that we have learned about this condition

since favours this theory more and more.* The researches of Hamerton (1938) seem especially to favour this theory. Also, certain observations on human subacute combined degeneration seem to favour the same hypothesis (Schlesinger, 1920 ; Modes, 1922, *et al.*). Furthermore, from the work of Gildea, Kattwinkel and Castle (1930), of Zimmerman and his co-workers (1933, 1936, 1937) and others, it is known that avitaminosis (of A as well as B2), is able to provoke in dogs and rats, not only peripheral nerve lesions but also degenerative lesions in the white matter of the spinal cord. Although these lesions, as far as the description allows of judgement, do not seem to be identical with those of subacute combined in man and apes, they prove, in principle, that deficiency can affect the white matter of the central nervous system.

These facts are, of course, no proof of the deficiency nature of the papillo-macular bundle degeneration, but they are certainly sufficient to admit it as a working hypothesis for further investigation. They would justify the attempt to produce, by systematic avitaminosis experiments, not only papillo-macular bundle degeneration but the lesions of subacute combined degeneration in apes. Up to now, avitaminosis experiments have been carried out largely with dogs and rats, animals in which spontaneous optic nerve lesions or subacute combined degeneration were unknown until now. It seems logical to try the experimental realization of these conditions in an animal which shows such a definite tendency to their spontaneous appearance, as the ape.

Summary

A spontaneous systemic degeneration of the papillo-macular bundle is frequently found in captive monkeys dying from different general diseases. In routine optic nerve examinations it has been observed in 8 out of 27 cases, most of these were of recent onset.

The optic nerve lesions which accompany most cases of spontaneous " encephalosis " and " myelosis " in monkeys (cerebral and spinal form of subacute combined degeneration), are also systemic degenerations of the papillo-macular bundle. They may be complicated by the appearance in the peripheral optic pathways of the same circumscribed, later confluent, patches of demyelinization which characterize the disease in the spinal cord and centrum ovale.

The frequency of the optic lesion and its often terminal character in different general diseases (generalized tuberculosis, gastro-intestinal troubles, cachexia, meningitis, etc.) suggests that its origin may be in a nutritional deficiency, and that this may also account for the lesions of subacute combined in monkeys.

* In a short abstract of a verbal communication Gärtner (1932, 1933), published a successful transmission of the condition in 8 cases by intracerebral or intramuscular inoculation of brain tissue and cerebrospinal fluid from affected cases. Unfortunately these researches have never been published in detail, and it is impossible to be sure of the following points : 1, whether the author was really dealing with the same affection or not. 2, whether an avitaminosis was excluded in his experiments or not. As he does not speak of controls there would be no proof that the inoculation caused the condition, it might have been caused by a coincidental deficiency in all these monkeys. Gärtner even mentions gastro-intestinal troubles and pathological lesions of the digestive tract in his cases, so that this communication gives no adequate evidence for an infectious cause of subacute combined degeneration in monkeys.

Our actual knowledge of human papillo-macular bundle degeneration seems to support this hypothesis.

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A CRITICAL REVIEW

THE TREATMENT OF MENTAL DISORDERS BY INDUCED CONVULSIONS

BY

A. KENNEDY

HISTORICAL INTRODUCTION

THE concept of the treatment of mental disorders by artificially induced convulsions owes its origin to the combination of two previously known facts. One of these was that some substances were able in toxic doses to bring about convulsions in man, without necessarily causing death, and that controlled convulsions could be produced by them in animals without apparent harm. The other was the observation that the development of spontaneous convulsions in persons suffering from schizophrenic psychoses had been followed in some cases by a rapid remission in the mental symptoms.

Although the validity of the supposed antagonism between epileptic and schizophrenic states has been recently much questioned, it was the attempt to utilize this antagonism for therapeutic purposes that formed the theoretical foundation of convulsion-therapy. Müller in 1930 had summarized the evidence for this hypothesis, and it was Nyirö who, in 1932, first attempted to make use of it by transfusing schizophrenic patients with the blood of epileptics. The lack of therapeutic success of this method suggested to Meduna the idea of actually reproducing the epileptic convulsions in his patients. In 1933, therefore, after preliminary experiments on animals had established that there was no gross damage to the nervous system after convulsions induced by toxic doses, Meduna gave 20 per cent. solutions of camphor to a group of schizophrenics, by the intramuscular route in gradually increasing doses, until convulsions were produced. Although in many cases the psychoses of these patients were of long duration, the results were sufficiently encouraging to warrant further trials. The very considerable technical difficulties involved in the use of camphor have led all but a few workers to abandon it as a convulsant, and Meduna's attention was early directed to the suitability of pentamethylenetetrazol, with which convulsions had been readily produced in animals. This drug possessed the convulsant properties of camphor with the advantages of solubility and suitability for intravenous use, together with rapid excretion and few toxic effects, and was used in 1933 in his next series of cases.

As with many advances in medical science, the idea of using camphor convulsions in treatment was not entirely a new one, and Glesinger, Havas, and

Meduna (1938) have collected some references to its use in early psychiatric literature. Leopold v. Auenbrugger, in 1764, advised in cases of *Mania Virorum* that a mixture containing camphor should be taken every two hours day and night. In 1781 William Oliver of London (quoted by Diethelm, 1939) recorded how a case of mania improved following convulsions brought about by the administration of large amounts of camphor given to induce rest ; while A. Weickhardt in his " Medizinisches Praktiches Handbuch " of 1798 advises that in cases of lunacy, camphor should be pushed to the point of producing vertigo and epileptic fits, after which point is reached, he says, the condition will usually clear up. G. Szekeres of Olmutz, in 1851, quotes Pauliczky as recommending that, in cases of insanity, camphor should be given in doses increasing by 5 grains until 60 grains are given daily, and that this dosage should be continued until fits appear. After the fits, he says, the patients will become lucid and commence to recover. References to the beneficial effects of convulsions on mental disorders also occur in the French literature of the eighteenth century, and it is clear that their therapeutic use has only now been revived after a lapse of almost a century.

If, in retrospect, the working hypothesis which led Meduna to develop this mode of treatment may seem debatable, the results recorded in the earlier publications commanded attention and led to a rapid extension of clinical trials. The Hungarian publications were soon followed in 1934 by others from Germany and Switzerland. It is probable, however, that other factors than those of distance and of language delayed further adoption of the method, especially in the English-speaking countries. The drastic nature of the treatment and its possible conflict with the traditional caution of English medicine produced a justifiable hesitancy to submit it to clinical trial. The attention of psychiatrists was also focused at that time on the claims of prolonged narcosis and of insulin therapy in schizophrenia, the latter being in use in England and America at the end of 1936. It was the congress on shock therapy at Münsingen in May 1937, the reports of which are now available in English (Katzenelbogen, 1938), that drew attention to the necessity for further serious trial, and shortly after this congress the first case-reports appeared in English from both sides of the Atlantic. Since then there has been a period of extensive clinical trial all over the world, and early enthusiasm has given place to a more seasoned evaluation of the uses and dangers of the method. The subject of convulsion-therapy has been under discussion at a number of conferences, such as that of the American Psychiatric Association (in 1938) and of the Royal Medico-Psychological Association in 1938, and a number of reviews have appeared (Thumm, 1938 ; Harris, 1938 ; Rees-Thomas and Wilson, 1938) which have allowed of some expression of opinion. These, with others, have been of considerable assistance to the writer in ascertaining current views as to the value of the method.

METHODS AND VARIATIONS—COMPLICATIONS

Technique.—Although there have been a great number of minor variations, the methods in use at most centres do not differ widely from the original technique of Meduna, which has been described too often for inclusion here, and is given in detail

in the Report of the Board of Control (Rees-Thomas and Wilson, 1938). Only the more striking variants will therefore be discussed. Some of the practical details will be referred to later in the section on the prevention of complications, while the psychotherapeutic aspects of treatment will also be left to a later section.

The majority of workers employ the buffered 10 per cent. solution and the usual initial dose is 5 c.c., to be repeated one minute later if no convulsion occurs. Dean (1938) allows for the slight tolerance which is usually seen by increasing the dose by 0·5 c.c. at every third injection, but the strength and duration of the fits is probably a better guide to future dosage. The tolerance developed to cardiazol is in contrast to the sensitization described as occurring with triazol 156, but it seems likely that the variations in the minimum convulsant-dose vary as much with the individual patient as with the convulsant used. Opinions as to the maximum safe dose vary a good deal. Kennedy (1939) has shown that the response of monkeys to intravenous injections of cardiazol is very closely similar to that of man when doses are given in proportion to the body weight. When a dose equivalent to 14 c.c. in a man of average weight was given to these animals, a severe status epilepticus developed, though the animals eventually recovered. Although the experiments of Ligterink (1937) indicate that the fatal dose is probably about 30 c.c., considerably more has been given in the course of treatment without ill effect, such as the 46 c.c. of Meduna (1938). Rees-Thomas and Wilson suggest that 16 c.c. should be the maximum single dose, to be repeated once, a minute later, if no convulsion ensues. The usual practice is to give the injections three times a week.

In an attempt to reduce the dose necessary to produce a convulsion, by bringing about a metabolic state which favours convulsions, Friedman (1937) introduced the method of alkalization and hydration. This consists in giving a minimum fluid intake of 2 litres per day, together with a high alkaline ash diet and sufficient alkali by mouth to keep the urine constantly blue to litmus. The careful studies of Dean (1938) show that although patients in the alkaline-hydrated state may show muscular hyperirritability, there is little significant effect on the dosage of cardiazol, while the diet is very distasteful to the patient and may cause a loss of weight.

The majority of patients, while recalling nothing of the actual convulsion, retain at some period of the treatment a vague feeling that it has been an unpleasant experience, and this may cause a considerable anxiety and dread of subsequent injections. The patient may be spared much of this apprehension if care is taken that he does not see other patients having treatment and that he is not kept in suspense by unnecessary preliminaries to the injection itself. There is no doubt that this complication is less frequent if care is taken to avoid giving subconvulsant doses, which produce acute fear-states that the patient can actually remember. The method of treatment in a series of separate rooms has the advantage that the patient need not know about the injection until it is actually about to be given. Although the use of barbiturates is precluded because of their inhibiting effect on the convulsions, hyoscine has no such effect, and used alone (Kennedy, 1937 ; Cohen, 1938) or with morphia (Cook, 1938) assists materially in causing the patients to await the injection calmly and to forget the period immediately preceding it. Cohen has observed that hyoscine even somewhat increases the tendency to convulsions, allowing of a slight reduction in dose. The elimination of this dread of the treatment is one of the advantages of the " summation " treatment of Georgi (1937), in which the convulsions are induced when the patient is in early insulin coma.

Use of Convulsants other than Cardiazol.—One of the difficulties encountered by all the workers with cardiazol is that many catatonic patients with general vascular hypoplasia have very poor veins. Further, owing to the rather high pressure at which the solution is injected, thrombosis due to small paravenous leakages is fairly common, even if it has been minimized in reporting results. Cardiazol when given intramuscularly, is rather uncertain in its action and often causes a period of restless anxiety before the onset of the fit, due to its slow absorption.

Behrens, Dinkler, and Woenckhaus (1937) had shown that triazol 156 could be used to induce fits in predisposed subjects, and Walk and Mayer-Gross (1938) applied it to convulsion-therapy. They found that the 5 per cent. solution had no sclerotic action on the veins when given intravenously, though this has been since questioned (Uebler, 1939), and that it was absorbed sufficiently by the intramuscular route for this method to be practicable. It also has the advantage that less than 2 c.c. of the solution is usually necessary to produce a convulsion. Walk and Mayer-Gross (1938) found that the intramuscular dose was one and one-half to two times the intravenous dose, which is rather less than the proportion necessary for cardiazol. Braunmühl (1938) emphasizes the importance of accurate dosage and has determined a constant for its calculation from the body-weight. The average commencing dose is about 1·4 c.c. With intravenous triazol the period of induction of the fit is more prolonged and it is not always easy to be sure whether a complete convulsion will occur after the injection. Secondary convulsions are common and in some cases multiple fits occur. These are not necessarily harmful and it has been suggested that they should be induced deliberately ; in any case, they can usually be stopped by injections of phenobarbitone. It is probable that triazol is eliminated more slowly from the body than cardiazol and great caution has to be taken in giving supplementary doses when no convulsion has occurred after the first injection, as accumulation of the drug may cause delayed multiple convulsions. The margin of safety is clearly less than with cardiazol and a second dose should be of only one-third of the original quantity. Vomiting is a common complication after triazol convulsions, but it is easily prevented by premedication with atropine. When triazol is given intramuscularly, the time relations of the convulsive phenomenon are greatly lengthened, and Walk and Mayer-Gross have shown that, when it is dissected in this way, there are marked individual differences in the pattern of reaction. In some cases prolonged twilight-states occur, and these seem to be equal in therapeutic effect to the convulsions. The amnesia after triazol seems always to be greater than with cardiazol, and may occur even when a subconvulsive dose is given. It is for this reason, probably, that there is less fear of the injections with triazol, and it is more suitable for apprehensive patients. Braunmühl is of opinion that triazol gives better results with long-standing cases than cardiazol, which he prefers for recent cases, and that it is also more suitable for combined therapy with insulin than cardiazol.

A number of other substances have been suggested or used as therapeutic convulsants. Advantages are claimed for picrotoxin, suggested by Burn (1939) and used clinically by Low, Blaurock, Sachs, Wade, and Ross (1939). These workers found that there was an even longer interval between the injection and the convulsions than with triazol, and that multiple fits were common, but could be prevented by an intramuscular injection of seconal after the first convulsion. They report that there was practically no fear in their cases, and patients who had had cardiazol as well, preferred picrotoxin as it caused less unpleasant sensations. The use of monobrom camphor, which has been used extensively in animal experiments and does not appear to have toxic effects, such as are seen with thujone, was advocated by Wortis, Coombs and Pike (1931), but no clinical reports have appeared.

A number of Italian workers have obtained satisfactory results with 5 and 10 per cent. solutions of ammonium chloride (Bertolani, 1939 ; Maffa, 1939 ; Baraldi, 1939). No untoward complications have been recorded and the reduction in cost makes this drug seem very attractive.

Much attention has also been paid by Italian workers to the possibility of producing therapeutic convulsions by means of electric shocks. Cerletti (1939), after numerous experiments with dogs, has, with Bini, developed a method by which the current is applied by means of scalp electrodes. Their apparatus consists of two circuits, one of which is used to measure the resistance offered by the patient's head, in order to determine the current required, while the other is used to carry the shock itself. In a majority of cases an intensity of 150 volts with an alternating current of

comparatively low quantity is sufficient to bring about a convulsion. Kalinowsky (1939) has pointed out that the convulsive threshold is lowest if the electrodes are applied over the area 6 α β of Foerster. The great advantage of this method appears to lie in the absence of unpleasant sensations in the patient. If a subconvulsive potential is applied, a petit mal reaction is obtained of which the patient has no memory. No fatality or case of burning has yet been recorded, and the surprisingly low intensities used suggest that the method is safer than might at first be thought. The development of this method is clearly of great theoretical importance, as, if the therapeutic effects are in every way similar to those of chemically induced convulsions, the effect of the convulsant agent *per se* can be eliminated from consideration.

Combined therapy with insulin has attained considerable popularity and the modification classed by Küppers as " summation " treatment, in which the convulsions are induced usually an hour and a half after the administration of a coma dose of insulin, is the most popular. The technique of Georgi and Strauss (1937) is most usually employed, and it is generally believed that the greatest benefit results if the cardiazol is given from the commencement, as soon as the insulin dose is established. The advantages of this method have been summarized by Russell (1938), who stresses especially the absence of fear in the patients and the fact that only small doses of cardiazol are necessary to produce fits, if it is given at the " turning-point " described by Georgi. Vomiting is a rather troublesome complication after fits induced at this period, but Russell says that this complication can usually be prevented if the stomach is emptied before the treatment is commenced and if atropin is given before the injection. Larkin (1938) recommends that a small quantity of glucose be given intravenously after the cardiazol, to prevent any possible collapse after the convulsion.

Indications for Convulsion-Therapy in Schizophrenia

Unfortunately there are no data available in which the case-material is classified into types, and all that can be given on this subject is a statement of general opinion as expressed in the conferences before mentioned and in the impressions of the different writers. There seems to be general agreement that, of the schizophrenic cases, those with catatonic stupor react best of all to convulsions, just as early paranoid cases react best to insulin. A special group of schizophrenics which reacts exceptionally well includes those having depressive symptoms. Cases of dementia simplex are generally agreed to react poorly to either method, and cases of paraphrenia occurring at the upper schizophrenic age-group appear to do little better. It is to be remembered, however, that these are the least prognostically favourable groups from the point of view of spontaneous remission. It might be fair to say that the prognosis of a given case under shock-therapy varies with its prognosis for spontaneous remission, but that the shock treatment affords an increased possibility of early remission. In choosing which method is to be employed, convulsion-treatment should be considered where the manifestations of the disease are essentially psychomotor or affective, and insulin-therapy where the disorder is predominantly intrapsychic.

Convulsion-Therapy in conditions other than Schizophrenia

The range of mental reaction-states which are benefited by convulsion-therapy does not appear to be limited to schizophrenia. Meduna has pointed out that there is little prospect of success where there is a poor heredity in a case

of schizophrenia, but that the outlook is best where the illness is the result of adverse circumstances : i.e. when it is reactive rather than endogenous. It is thus of interest to find that other states which may be in even greater part reactive have been found to respond favourably to convulsion-therapy. Favourable results have been reported in manic-depressive psychosis, in cases of involutional depression, and in the small number of cases of severe hysteria which have so far been published the effects reported have been very striking indeed.

Cook and Ogden (1938) were impressed with the favourable results in cases of schizophrenia which showed depressive features, and have published the results in a small series of cases of affective psychosis. It was noteworthy that in their cases the change in mood occurred after only a few injections and that a full course was not necessary. Similar results have been recorded by Goldstein and his co-workers (1938), Low and his co-workers (1938), Bennett (1938), Webster (1938), and Wyllie (1938), while Verstraeten (1938) has had favourable results with cases of involutional depression. The general impression at the moment is that convulsion-therapy is unlikely to have a specific effect on these psychoses, but that it is able sometimes to determine a favourable change of mood in cases where such a change may be expected to occur sooner or later. It is felt that in the present state of our knowledge the indiscriminate use of convulsions in affective psychoses is unjustified, even though the risks involved are not very great, and that the use of this method should be reserved for cases in which effects are likely to be permanent. Such circumstances would occur if a case showing no deterioration was lasting much longer than anticipated, or if the patient, by reason of excitement or agitation, was becoming exhausted. Other indications would be the occurrence of severe depressive stupor which interferes with nutrition or the occurrence of repeated attempts at suicide. The case of involutional depression is rather different. Although recorded material is as yet rather scanty, the opinion is gaining ground that the prognosis after convulsion-therapy in this condition is distinctly better than its prognosis with conservative therapy, and that a certain amount of risk is here justified. The effect of treatment seems to be upon the affective element of these psychoses.

Harris and Birnie (1938) have shown the value of convulsion-therapy in cases of stupor of all types, and have pointed out that the outlook in depressive stupor is always potentially good, even when the condition has been present for a long time, as there is here no process of deterioration which causes the patient's chances to become less as time passes by. In such cases Berrington has found the use of intravenous sodium amytal, according to the technique of Bleckwenn (1931) a valuable means of temporarily reviving the patient in order to assess the degree of deterioration and thought-disorder. Harris and Birnie (1938) observe that stuporose patients who show a good transient awakening with amytal are likely to respond to convulsion-therapy. Apart from the production of complete remissions it is felt that the use of convulsions is often justifiable if it is able, as it so often is, to end the stupor, with its attendant nutritional and nursing difficulties. Even if the patient cannot be discharged from the

institution afterwards, as the result of the treatment he often becomes a more useful and stable inhabitant of it.

It may perhaps be more helpful to regard convulsion-therapy not as a specific remedy for a single type of psychosomatic disorder, but rather as acting on a mental symptom-complex which is common to most of the conditions which it can affect favourably. The exact features of this symptom-complex must vary according to its setting, but inhibition and a depressive affect are certainly two of the features prominent in cases which benefit from convulsion-therapy. Thought-disorder, on the other hand, seems rarely to be improved except in so far as it is a consequence of inhibition. Where the patient's reaction-form as a whole is a composite one, the degree of its recovery may depend on the amount of that component in its make-up which is favourably affected by cardiazol therapy.

The literature contains references to a small number of cases of gross hysteria which have been treated with cardiazol, and Low and Verstraeten, Cook and Ogden (1938), and Read and his co-workers (1938) all record successful results. The writer feels that there is room for further investigation on these lines in cases of degenerative hysteria without epilepsy which have become inaccessible to psychotherapy and other measures.

Complications of Convulsion-Therapy and their prevention

It is unfortunate that with the exception of Meduna's reports, the earlier papers on convulsion-therapy, in their enthusiasm for the method, gave little if any prominence to such complications as they observed. Later publications have not been entirely satisfactory in this respect ; Ross (1939), for instance, in the report on 1,500 cases treated in the New York State Hospitals, records only complications which proved fatal. Apart from the results of an enquiry into the incidence of the more serious complications in the Dutch hospitals given by Pameijer (1938), there is little material from which to form a reliable estimate of their frequency. It is clearly impossible to avoid complications with a method which produces such violent effects on the organism. In visits to hospitals in Europe and in the United States the writer has had the opportunity of discussing the subject with many workers. The general opinion is that, while various non-fatal complications are very common indeed, they are mainly of a preventable kind. Their number tends to diminish as the practical experience of the hospital staffs increases.

Immediate Complications.—Minor complications occur mainly at the time of the actual convulsions. Venous thrombosis, while less frequent since the use of the 20 per cent. cardiazol solution has been abandoned, is a difficulty which is frequently minimized, but is not to be forgotten if the incidence of pulmonary abscess is to be lowered, as this is presumably due usually to the mobilization of thrombi from the site of injection. It is claimed (Walk and Mayer-Gross, 1938) that this complication is less common with triazol, though this is denied by Uebler (1939). The possibility of " speed-shock " has received prominence in view of the high speed at which the solution is usually injected

but although the work of Hirschfeld, Hyman, and Wagner(1931) would indicate that with practically any substance injected rapidly the occurrence of anaphylactoid collapse is theoretically possible, there is as yet no recorded instance of this having occurred. Vomiting at the termination of the convulsion is not common with cardiazol alone, but is very frequent with triazol and in the insulin-cardiazol "summation" treatment of Georgi. In triazol treatment the giving of atropin and a small quantity of glucose before the convulsion will usually prevent this. While long apnœic periods at the end of the clonic stage of the convulsion may give rise to anxiety, they do not appear to be dangerous if the airway is kept clear. Injection of lobeline has been suggested if artificial respiration is ineffective, but it must be remembered, as Draper and Whitehead (1939), have recently pointed out, that respiratory stimulants may have a depressant action where anoxæmia is extreme.

The most important immediate complications are the injuries which the patient may sustain as the result of the violence of the muscular contractions during the fits. It would seem that the actual pattern of the convulsion predisposes to certain injuries in cases where the bones or joints are vulnerable, and it is noteworthy that these injuries are not those found in idiopathic epilepsy. The very frequent dislocation of the jaw, which is regarded by many workers as inevitable in a small proportion of cases, is not often seen in epilepsy, and is clearly related to the sudden opening of the mouth which is so characteristic of the onset of the cardiazol convulsion. While it is readily reducible and usually causes little trouble, there is no doubt that its incidence is lower where the nurses have gained experience. Dislocation of the shoulder is a more serious but less frequent complication, though its frequency in Winkelman's (1938) series of cases led Rechtman and Winkelman (1939) to devise a special apparatus for the patients to wear in order to prevent it.

The most frequent major injuries reported in the literature are as follows : Fracture of Neck of Femur : Pameijer 5, Walk 2, Jansen 2, Müller 2, Ross 1, Horn 1, Nyberg 1, Kerstens 1, Rees-Thomas and Wilson 1, Somers *et al.* 1 ; of Humerus : Pameijer 3, Wulften 1, Kraus 1 ; of Scapula : Pameijer 3, Stahli 2 ; of Thoracic vertebræ : Stalker 1, Wespi 1, Polatin *et al.* 22, Palmer 5. Dislocation of Shoulder : Winkelman 3, Somers *et al.* 2, Cohen 1, Pameijer "several," Harris and Birnie 1.

Meduna (quoted by Rees-Thomas and Wilson) in his reports of 1,244 cases treated in 29 American hospitals, records 27 fractures ; while Pameijer found 15 in 1,200 cases. From this limited material the incidence of major fractures is 1, 7 per cent., a matter of some seriousness when it is considered that fracture of the neck of the femur may be the most frequent of these. In two recorded cases (Ross, Walk, and Mayer-Gross) fracture of the femur contributed materially to a fatal issue.

Until very recently there were but two recorded cases of vertebral fracture, those of Wespi (1938) and Stalker (1938), both at the 6th thoracic level. In view of the high incidence of backache it seemed probable that minor non-bony injuries to the vertebral column might be common, but these were not thought likely to be dangerous. The work of Polatin, Friedman, Harris, and Horwitz,

if confirmed, and little more confirmation is needed, may make us feel less secure about such injuries. These workers investigated 51 cases radiologically and found thoracic compression fractures in 22, or 43 per cent. The fractures were not necessarily accompanied by backache, and the degree of injury bore no relation to the amount of subjective complaint. It is evident that the mid-thoracic vertebræ are the vulnerable points and that the anterior portions of the vertebral bodies are crushed in the sudden anterior flexion at the onset of the convulsion. It is clear that a large number of cases will have to be examined and some postural means, such as that of Bennett and Fitzpatrick (1939), found of avoiding this complication if the treatment is to be made safe. Convulsions produced during spinal anæsthesia might prove a laborious, though safe, solution of this problem. Palmer (1939) has also found a high proportion of vertebral fractures in patients examined radiologically at the conclusion of treatment. It is notable that in spite of these findings only the two first cases recorded were seriously inconvenienced by the presence of the fractures, many radiologically positive cases having no symptoms at all. If fractures are to be prevented, it is clear that care must be taken to exclude cases which, by reason of prolonged inactivity, of age or of inadequate nutrition, are vulnerable to fractures on account of decalcification, and also to exclude the possibility of predisposition to dislocation or of bone disease in cases which are chosen for treatment. It is also necessary to keep the dosage of the convulsant down to the minimum necessary to produce a fit and thus avoid the severe ophisthotonic convulsions in which these accidents often occur. A very important factor indeed is the training of the nurses who handle the patient during the convulsions to know of the possible injuries, and especially in the case of dislocations, to know how they may be prevented.

The occurrence of status epilepticus is uncommon with cardiazol and repeated convulsions are rarely seen as they are with triazol. This complication is not usually dangerous and can be ended with intravenous injections of phenobarbitone.

Late Complications.—The second group of complications includes those which appear after the actual convulsion is over, and some of these, though uncommon, are serious. There is a tendency, noted especially by Harris (1938), for septic conditions such as boils, tonsillitis, and whitlow to appear during treatment, and, in particular, patients seem susceptible to lobar pneumonia. Among 523 cases, Ross (1939) described three fatal cases of pneumonia in the three-week period following a course of treatment and one fatal case of pulmonary abscess. Van Craaf, Montfrans, and Brouwer (1938) describe four cases in which acute lesions demonstrable by X-ray appeared during treatment but subsided in a few days. These may have been embolic in origin. Pameijer (1938) describes seven non-fatal cases of pulmonary abscess, and there is reason to believe that this is the most frequent pulmonary complication. This worker also records seven cases in which latent and unnoticed pulmonary tuberculosis appeared to have been activated by the treatment. Harris and Birnie (1938) record a similar case among 18 cases of stupor treated with cardiazol. The question whether it is justifiable to treat

young subjects with latent tuberculosis was discussed at the Munsingen Congress (Thumm, 1938 ; Meduna, 1937). It was thought then that, where the illness was of short duration and the prognosis good, and yet remission did not seem to be coming about spontaneously, it might be justifiable to take a slightly increased risk. The prevention of pulmonary complications, therefore, lies in the exclusion of cases of pre-existing pulmonary disease, the avoidance of aspiration of foreign bodies and septic material while the cough-reflex is absent, and in care in avoiding the mobilization of thrombi from the site of injection, which might produce small emboli and later pulmonary abscesses. It is essential that the patient should be in bed a few days before treatment begins and that the temperature and pulse should be carefully recorded during this period to exclude minor infective foci. Dental sepsis, and especially teeth which may break, must be attended to before treatment is commenced.

It seemed at first from the observations of Meduna, based on the electrocardiographic work of Dobozy and Lax (1936) that convulsions had little adverse effect on the heart. Geraudel (1939), however, has studied the electrocardiographic records in the period following the fit in a series of cases and found that a temporary inversion of the T-wave in two leads occurred fairly often. He regards it as a sign of myocardial distress and an indication for cessation of the treatment. Schmitt (1939) has collected 68 records commencing at the clonic phase of the fit and found a number of abnormalities. In some cases there was a simple sinus tachycardia, similar to that seen in Graves' disease, while in others there were extrasystoles, both auricular and ventricular, which sometimes produced a pulsus bigeminus. In 10 of these cases the records were normal before treatment, and she concludes that cardiazol injections are able to produce minor myocardial lesions. McAdam (1938) also found disturbances in the electrical heart record, but these only persisted for a short period after the convulsion and were rather similar to the recent findings of Erickson (1939) in epilepsy induced during intracranial operations. McAdam has also observed that a reduplicated mitral second sound can often be heard in the period following the fit.

Pameijer (1938), in his investigations into the complications in 1,200 cases in Holland, encountered many cases of cardiac weakness during treatment and reports two cases of death due to this cause. Dick and McAdam (1938) have reported three cases of auricular fibrillation precipitated by the convulsions. It is clear, nevertheless, that cardiac complications are not frequent and that their incidence can be reduced, to some extent at least, if cases are excluded whose myocardial powers are thought unequal to and unprepared for the considerable effort involved in the treatment.

Complications in the Nervous System : Adverse Mental Changes.—In spite of the great rise in blood-pressure which occurs during the convulsions, the experimental evidence of minor lesions, and the apparent incidence of most of the changes on the nervous system, gross disorders of this system appears to be rare and there is no case on record of severe vascular accident as a complication. One complication which was much feared in the early stages of the treatment was not recorded at all until Hobson (1938) described a case of

spontaneous epilepsy commencing after a course of cardiazol therapy. In this case the patient had five spontaneous fits after treatment had been discontinued, but they ceased after a month and with their disappearance the patient, who had improved mentally, relapsed. It does not appear from this that induced convulsions are likely to precipitate a permanent convulsive tendency.

One is apt, when considering the results of a series of cases, to pay most attention to the mental changes in the improved group. Examination of the unimproved cases, however, frequently shows that unfavourable changes occur and that the mental state has in fact been made worse, at least for the time being. Harris (1938) remarks that cases of catatonic stupor which do not recover frequently pass into a state of excitement which makes them difficult to nurse. Nightingale (1938) observes that cases that have been quiet and friendly may become mischievous and interfering after an unsuccessful course of convulsions. The unfavourable psychical effects of convulsions may be divided into two groups. First, increases in the psychotic manifestations and changes in behaviour which cause difficulties in nursing ; secondly disorders of memory ; and thirdly the rather vague personality changes observed in some remitted cases which are regarded by some as evidence of mental deterioration. Of the unfavourable psychical changes observed some are seen in connection with the actual injection and the period which follows it and others after the course of treatment is over. The first group includes the states of panic which occur when a subconvulsive dose is given. The states of excitement following the convulsion, are comparable to the fugues and furors of epilepsy, as the patient has little memory of what has happened. It is generally agreed that the anxiety attacks are to be avoided, as the patient usually has a very unpleasant memory of them and is likely to dread a repetition. The fugues, if the patient is prevented from harming himself, appear to do no harm, but close observation is necessary as suicidal attempts or attempts to run away are always possible. It seems likely that the incidence of such behaviour might be reduced, if care is taken that the patients are not made apprehensive before the injections by hearing other patients and thus having ideas of escape and hostility implanted in them, to be released in the post-convulsive period. Most workers have found that patients who have been stuporose or quiet often pass, during treatment, through a stage of excitement in which they are inco-operative and sometimes violent before improvement occurs. It is not unreasonable to expect that the first emotional responses after a long period of restricted affectivity might be somewhat uncontrolled, and Dynes' (1939) view that such reactions should be an indication for termination of the treatment seems a little unjustified. This worker observed that in three out of 10 unfavourable cases excitement and antisocial behaviour went on after the course was over, and Berrington (1939) and Harris (1938) have made similar observations. It appears that apart from these periods of excitement, which in Dynes' cases had subsided within 2 months, the form of the psychosis can be changed in a way that makes the patient more difficult to look after. It is at least as likely, of course, as Ross (1939) has pointed out, to have the opposite effect, difficult patients, while not

becoming fit for discharge, being able after treatment to work contentedly within their institutions.

A number of workers (Balta, 1939 ; Canseco, 1939 ; Dynes, 1939 ; Tooth and Blackburn, 1939 ; Weitbrecht, 1938) have now drawn attention to disorders of memory observed after courses of convulsions, and this, together with certain personality changes (Berrington, 1939) has been adduced as evidence of mental deterioration in the patients. The evidence for this will be dealt with in a later section.

Reported Results and their Significance

Although over 5,000 cases have now been reported in the literature, study of the available figures makes it evident that lack of uniformity in the collection of the material has practically destroyed its statistical value. As the method has gained more extensive application, the high recovery rates reported by earlier enthusiasts have not been substantiated ; and even when consideration is restricted to cases of 18 months' or less duration, the remission rate continues to decline as more reports are added. In a review of results in these early cases up to the end of 1938, Reitmann (1939) has shown that the percentage of remissions at different hospitals varies from 7 to 100 per cent., and in a study of similar figures available in English-speaking countries, Kennedy (1939) has shown that the variation in results is far in excess of any that could result from chance distribution of cases. Not only are there great variations in the remission rate from year to year, but the total rates from different countries vary from 79 per cent. in Italy to 39 per cent. in Germany, a discrepancy which is again far too great to be accounted for by chance differences in case material. The gross rate for complete remissions in 1,572 English and American cases of less than 18 months' duration was 38 per cent. ; when cases of up to 10 years' duration were included, this percentage fell in most series to a figure not far in excess of that for spontaneous remission in comparable institutions. Apart from the errors introduced by the propagandist type of report, based on selected cases, the lack of uniform classification of the different grades of improvement has made only the numbers of complete remissions suitable for statistical treatment. Only rough impressions can be gained as to the amount of improvement in other cases, a matter for regret, as it is evident that a large number of patients are greatly improved, even though they are not capable of complete social rehabilitation. It is to be hoped that the suggestions of the Board of Control (Rees-Thomas and Wilson, 1938) for a uniform classification will be adopted. The scheme advised is a modification of Müller's (1937) classification, cases being divided into complete remissions, incomplete remissions, partial remissions, unimproved cases continuing to need hospital care, and deaths.

While the general rate for full remissions in early cases may be as high as the 38 per cent. quoted above, there is no doubt that in cases of over 3 years' duration the prospects of reversal of the schizophrenic process are slight indeed.

A difficulty which has not received adequate attention is the great frequency

of relapse after treatment. The importance of this can only be estimated in prolonged catamnestic studies such as those of Lehoczky, Eszenyi, Horányi-Hechst, and Bak (1939) are made. It seems probable that such studies will give a far more valuable impression of the effects of treatment than statistics based on the present methods of recording results. The frequency of relapse is very striking, and though it was early pointed out by v. Meduna, it has as yet been inadequately studied, apart from the work of the Hungarian schools.

In spite of the possibility of over-estimation, there seems little doubt that in most hands convulsion therapy has given results considerably better than the spontaneous remission rates for comparable case material. If comparison is made between the results of convulsion therapy and the spontaneous remission-rate at psychiatric clinics on the one hand and at hospitals for chronic cases on the other, the remission-rate after convulsion treatment is usually significantly higher than that occurring after the usual methods of treatment. Guttmann, Mayer-Gross, and Slater (1938), in order to obtain, for purposes of comparison, the remission-rate for methods other than shock-therapy in a prognostically favourable group of cases, followed up 280 schizophrenics admitted to the Maudsley Hospital and found that rather more than one-third recovered. This must represent the highest possible spontaneous remission-rate, and any treatment which improves on these results must be regarded as introducing a new therapeutic factor. Although convulsion-therapy may have done this, the margin cannot be a large one. Strecker (1938) has collected the spontaneous remission-rates from 11 sources in the literature, with a total of 581 cases, and finds an average of 24 per cent. When compared with the general results after convulsion therapy in all types of case, both recent and chronic, this again would indicate that the method may offer an improved therapeutic attack, though the difference is not a striking one. It is the speed of recovery, when it occurs, that has made the results appear more striking than they are.

In addition to comparison with spontaneous remissions, it is of interest to compare the results of convulsion therapy with those obtained by the two other methods which have been prominent in recent years, insulin shock and prolonged narcosis. In the survey published by Küppers the author is of opinion that the difference between the results of insulin therapy (30 per cent.) and cardiazol therapy (53 per cent.) is not to be taken too seriously as a comparison between the two methods. In their survey of results available up to April 1938, Rees-Thomas and Wilson come to a similar conclusion, and observe that those workers who are successful with either treatment tend to achieve comparatively poor results with the other, and that effective comparison is not likely to be obtained until a number of workers have had time to become familiar with both methods, and to have used them side by side in the same hospital. Reports from America indicate a similar state of affairs. In the State Hospitals of New York, Malzberg (1938) found a recovery rate of 23 per cent. with insulin therapy for cases of less than 1 year's duration, while an analysis of Ross's (1939) figures for slightly different material yields a percentage of 21 per cent. Using case material from the same hospitals, this worker obtained a remission-rate of only 10 per cent. for cardiazol treatment. This result has to be compared with

50 per cent. the remission-rate for all material published elsewhere than in New York State. It is evident that, although the results obtained by both insulin and cardiazol are better than the spontaneous remission-rates for the type of hospital from which they are obtained, it is not yet possible to make a fair comparison between them. It is noticeable that the results from psychiatric clinics are usually better with cardiazol, while those from mental hospitals are better with insulin. A possible cause for this difference may be the fact that, for legal reasons, paranoid cases, which are generally regarded as more suitable for insulin treatment, are more often sent to mental hospitals than to psychiatric clinics.

In the case of prolonged narcosis it is easier to make a comparison. The results obtained by the Zurich school, summarized in the papers of Klaesi (1922), Oberholzer (1927), Lutz (1930), and Monnier (1936), show that 62 out of a total of 258 cases were rendered fit for discharge by this treatment, i.e. 20 per cent., while the larger series of Meerloo (1933) shows a recovery rate of 33 per cent. in schizophrenic cases. These results are clearly not so high as the general level of the results of shock-therapy. The impression of English workers with this method of treatment is given by R. D. Gillespie in a critical review (1939) in which he observes that the remission-rate in recent psychoses does not exceed the spontaneous recovery rate, and that its principal use is to shorten the duration of illnesses which have a tendency to periodicity.

In general it is probably fair to say that patients who are constitutionally poor material are not likely to respond well to convulsion therapy or to any other therapy at present available. As Wortis (1936) has pointed out, the same rules for prognosis hold good now as before the introduction of shock-therapy. The evidence points to the fact that, when a case is likely to remit according to these rules, the appropriate method of shock-therapy will very often determine that remission and will bring it about earlier than any other method of treatment at present known.

Clinical Observations and Experimental Work

Since its origin, there has been an intense interest in the theoretical aspects of convulsion-therapy, and the experimental work that has been carried out has thrown a stimulating but sometimes confusing light on some of the problems of schizophrenia and of epilepsy.

Histopathology

The literature on the histological effects of induced convulsions is not yet very extensive and is confined to experimental work in animals, as no autopsy material has so far become available. Meduna in 1936 described the appearances seen after experimental camphor poisoning in rabbits, and recorded diffuse changes in the cell masses of the medulla and cerebellum. These changes consisted of vacuolization of cell protoplasm, chromatolysis of the Nissl bodies, and irregular staining and displacement of the nuclei, together with complete disintegration of some of the cells. There was little change in the

cerebrum and the distribution of the lesions as a whole suggested a toxic rather than a vascular origin. Some of these changes, at least, were attributable as much to the effects of the camphor as to the results of the convulsions *per se*. The cell changes themselves, too, were of the nature of the " primary irritation " of the German schools, which may be produced by either vascular or toxic causes. Kastein (1938) found that the most marked effects after cardiazol convulsions were in the cerebellum, cornu ammonis, and habenular region and considered them to be vascular in origin. Stender (1937), also working with cardiazol convulsions in rabbits, found no changes of importance, while Morsier, Georgi, and Rutishauser (1937) found only a hyperæmic picture, probably due to terminal asphyxia. Nyberg (1937), in his careful studies of rabbit brains, demonstrated perivascular infiltrations which, in his illustrations at least, suggest the spontaneous encephalitis so common in that animal rather than a specific effect of the convulsions.

Reitmann (1938), in experiments on dogs, found circumscribed microscopic parenchymatous hæmorrhages distributed throughout the cortex. The vessels in these hæmorrhages appeared to be intact. He also found ischæmic foci and areas of diffuse disturbance similar to those found by v. Meduna and Kastein. These findings suggested to him that there was a functional disturbance of the cerebral blood vessels. Scholz (1936) comes to a similar conclusion, and, from experiments on kittens in which the changes were more marked than in adult animals, regards the young nervous system as more vulnerable to the changes produced. In a later publication, Dreszer and Scholz (1939), using the benzidin method of Pickworth (1938) on cats, found differences in vascularity in animals killed at different stages of the convulsions. They conclude from these observations that a preliminary cerebral anæmia is followed by an hyperæmia during the actual occurrence of the convulsion. In his studies of the brains of animals subjected to convulsions from monobrom-camphor and thujone, Opper (1939) found areas of diffuse degenerative change scattered throughout the cortex, the cornu ammonis and basal regions being largely spared.

Strecker, Alpers, Flaherty, and Hughes (1938) examined the brains of monkeys in which a series of convulsions had been induced. They found small subarachnoid hæmorrhages in four out of seven animals, especially over the frontal regions, and in three animals there was vacuolization of the cytoplasm of the cortical cells. These workers remark on the slightness of the changes, especially in view of the fact that the total duration of the convulsions in these animals was far in excess of that to which patients are exposed in the longest courses of treatment. The majority of workers have regarded the histological findings as consistent with the effects of gross functional changes in the cerebral blood vessels, and especially of vascular " spasm." Ricker (1927) has, however, pointed out that the histological after-effects of vasoconstriction and of vasodilatation with vascular stasis cannot confidently be differentiated, and Meyer (1939) regards the evidence as insufficient as a basis for theorization as to the mechanism of causation. While some authors (Tooth, Dynes, Balta) have regarded the amnesias and other disturbances of mental function after cardiazol convulsions as related to brain-damage, such as is suggested by these histological

pictures, Spielmeyer and his pupils have pointed out that there are wide discrepancies between clinical and histological findings in such cases, and it is at present unsafe to accept the histological evidence as in any way explanatory of the clinical observations. It is upon the histological evidences of cell destruction, nevertheless, that Stief has based his theory of the action of convulsions by the therapeutic decimation of the cortical cell-units. It must be remembered, too, in interpreting these results, that the evidence available is based on experimental material and may bear little relation to the effects of convulsants in the smaller therapeutic doses. There is clearly room for much further work before the meaning of these data becomes clear in the light of other experimental approaches to the subject.

Convulsions and the Vascular System

The early observation that the cardiazol convulsion was accompanied by phenomena referable to changes in the vascular system has led to a revival of interest in the vascular theory of epilepsy, and if, at the end, this theory seems no more acceptable in the case of induced than of idiopathic epilepsy, it has at least stimulated some interesting experimental work. The subject has been investigated in a number of ways.

Blood-Pressure.—Meduna (1934), in his early work, demonstrated a rise of blood-pressure during the convulsion, the systolic pressure being most affected. It seemed likely that this was largely due to the muscular effort of the convulsion, as there was very little rise when a subconvulsive dose was given, even though cardiazol is a powerful cardiac stimulant. The experiments of Coombs and Pike (1931) with cats made this explanation seem a reasonable one. These workers had shown that with convulsions induced by monobrom-camphor, after a pre-paroxysmal fall there was a rise of blood-pressure with the onset of the actual convulsion, and that this rise could be abolished completely if the muscles were rendered flaccid by spinal transection or by curare. Meduna found no change in resting level after the convulsion but Harris (1938) found that this was often raised and Briner (1937) demonstrated a consistent rise of resting level throughout the course of treatment in many of his patients. In a recent careful study of 15 cases Guttmann and Reitmann (1939) have shown that after the injection there is a preliminary rise of pressure, but that at the time of onset of the fit there is a sharp fall, which is followed by a rise as the clonic stage comes on. They observe that this sudden rise after a fall represents a considerable strain on the cerebral vessels and may account for the frequency of small hæmorrhages in the histological picture. These workers also investigated the effect of non-convulsant doses of cardiazol and found that these caused a rise of blood-pressure dependent in degree on the dosage and on the initial level. They found that the nearer the dose approached the convulsant threshold the higher was the rise of pressure. This suggested to them that the rise in pressure might be a determining factor in producing the fits, especially as amyl nitrate and other hypotensors were known to inhibit them. When, however, the pressure was artificially raised by means of intravenous injections of benzedrine hydrochloride

fits did not occur with maximum non-convulsive doses, even though the pressure at which the convulsion occurred was greatly exceeded. It would thus seem that the rise in blood-pressure is not an important factor in determining the onset of the convulsion.

Vascular Spasm.—Reitmann (1938) in his histological studies on dogs, and later Dreszer and Scholz (1939), regarded the ischæmic necrosis found after convulsions as probably due to an intense temporary vasoconstriction. This view led Köst (1938) to try the effect of amyl nitrate, which has a reputed vasodilator effect on the cerebral vessels. By giving inhalations of amyl nitrite in ether he was able to inhibit the convulsions in all his cases. This result was confirmed by Denyssen and Watterson (1939), who used pure amyl nitrite and also sodium nitrite and histamine, and interpreted the results as indicating that the inhibition of the fit was due to prevention of cerebral vascular spasm. This neglected the possibility that, by its peripheral vasodilator action, it might cause sudden enlargement of the vascular field and divert much of the blood, and with it the cardiazol, that would otherwise reach the central nervous system in greater quantity. That amyl nitrite and similar drugs do, in fact, cause a significant dilation of cerebral vessels is by no means certain, though it is suggested by the work of Norcross (1938) on the cerebrospinal fluid pressure and by that of Wolff (1929). That histamine and amyl nitrite increase the blood flow through the brain, in some circumstances at least, is shown by the work of Schneider and Schneider (1934) but it must be recalled that this was carried out under barbiturate anæsthesia. Acetyl choline would appear to cause cerebral vasodilatation as judged by direct observation (Wolff, 1929) or by cerebrospinal fluid pressure changes (Norcross, 1938 ; Wolff, 1929). Assuming that two other choline derivatives, carbaminoyl choline (Doryl) and acetyl-β-methylcholine (Mecholyl) had a similar dilator effect, Watterson and MacDonald (1939) showed that these had an even more constant inhibiting effect on the convulsions. They found, however, the caffeine, which in animals, at least, is a cerebral vasodilator (Finesinger, 1932 ; Norcross, 1938), had no such inhibiting effect, and it is to be noted that caffeine has little, if any, peripheral vasodilator action.

Watterson and MacDonald (1939) point out that increase in the cerebral bloodflow may have at least as much to do with the inhibition of convulsions as the supposed prevention of vasoconstriction. The observations that ephedrine (Leibel and Hall, 1938), which is a peripheral vasoconstrictor, and sodium cyanide (Watterson and MacDonald, 1939), which also raises systematic blood-pressure, both inhibit the convulsions are perhaps in favour of this view, but the question of this mechanism is still a very open one.

Even if cerebral vasodilators are able to inhibit the convulsions it is by no means certain that these are actually caused by vasoconstriction, and the work of Forbes and Cobb (1938) suggests that sufficient constriction is not possible in the cerebral vessels to cause demonstrable lesions due to anoxæmia such as are the foundation of the vasoconstrictor theory. Nor does the work of Gibbs and Lennox (1938) make it appear that the reduction in blood-flow during a fit is enough to produce a very marked anoxæmia. It is thus of interest that Meduna (1937) records that it was not possible to observe surface vasocon-

striction in the cortex by direct vision at any period after the injection of convulsant doses of cardiazol. Many of those who favour the vasoconstrictor theory of the causation of convulsions regard a cellular anoxia as the intermediate mechanism. Even if vasoconstriction occurs and can be sufficiently intense to precipitate a convulsion, it seems unlikely that this effect could be produced in the short period which elapses between the time the drug passes the carotid sinus and the onset of the convulsion. Watterson and MacDonald (1939) have shown that the cardiazol reaches the brain only just before the onset of the convulsion. By injecting 0·5 c.c. of 2 per cent. sodium cyanide intravenously one second before the cardiazol, they demonstrated that the carotid-respiratory reflex (Bernthal, 1938) takes place little more than one second before the onset of the convulsion. The convulsant must thus pass the carotid sinus, where this reflex is initiated, only a moment before the fit begins. This observation suggests that, in accordance with the original view of Georgi (1937), the effect of cardiazol is a direct chemical one on the cerebral cells. If this is the case the different parts of the brain might be reached by the drug in order of their vascularity. This might account, perhaps, for the differences in pattern between the epileptic and the cardiazol fit and the greater constancy of the latter. The epileptic convulsion arising in foci in any part of the brain, and spreading by a process of conduction, might be expected to have a different and less constant pattern.

Blood-flow.—The most interesting work by this approach is that of Leibel and Hall (1938). These workers, using a modified thermoströhmur, recorded the changes in blood-flow in the carotid artery and in the meningeal branch of the jugular vein in a number of rabbits. They observed that, at the onset of a cardiazol convulsion, the blood flow in both vessels decreased to between one-half and one-fifth, after which it returned to the normal in an irregular manner suggestive of the presence of widespread arteriolar effects. These authors are of the opinion that this reduction in blood flow represents a severe and prolonged cerebral anæmia, and in view of the temporary beneficial effects of depressant substances on schizophrenic states this may be of importance in relation to the therapeutic effects of the convulsion.

In view of the observation that the peripheral circulation in catatonic patients with vascular stasis improved rapidly during convulsion treatment, it was of interest to know whether this circulatory improvement had any relation to the improvement in mental state. Harris (1938) observed, as had Briner (1937), that a gradual rise in blood-pressure accompanied the clearing up of peripheral stasis, but found that this was not necessarily accompanied by mental improvement. Many of his cases, however, were of long standing and the possibility of clinical improvement may have long passed.

Cerebrospinal Fluid Pressure.—A further method of investigating the vascular changes during induced convulsions is afforded by a study of pressure-changes in the cerebrospinal fluid. Niketic and Susic (1938) have demonstrated a sudden increase in pressure with the onset of the convulsion. This is indicative either of venous congestion due to the mechanical effects or of a very great vasodilatation, and may well be due to both these factors.

Effects of Convulsions on Catatonia-like States in Animals

Since studies in disorders of thought depend very largely on the interpretation of subjective experience, they cannot be approached by the method of reproducing the disease in the non-speaking experimental animal. Even if abnormal motor states could be produced resembling those of the schizophrenias in which motility is predominantly disordered it would be of some assistance. It is claimed that this can be done (de Jong and Baruk, 1930 ; Baruk, 1933), but this view is very open to question. A comparatively wide variety of substances are able to produce a cataleptoid state if given to appropriate animals, such as acetyl choline (de Jong, 1931), b.coli toxin (Baruk, 1933), carbon dioxide (Baruk, 1933), several benzene derivatives (de Jong, 1931) and somnifaine (Claude and Baruk, 1928). Similar states have been produced by thyroparathyroidectomy (Parhon and Urechia, 1908), by operative lesions near the third ventricle (Colucci and Sciuti, 1902) or retromammillary region (Ingram and Ranson, 1934), and by the intracistemal injection of deuternum oxide (Hermann and Barbour, 1938). None of these methods is at all constant in its effects, but with bulbocapnine, introduced by Peters in 1904, the effects, though brief, are fairly constant. While the syndrome produced by this drug has objective features in common with clinical catatonia, it has been pointed out (Schaltenbrand, 1929 ; Ferraro and Barrera, 1932) that it has symptom-components in common with other hypomotile states, such as post-encephalitic Parkinsonism. Some of the substances which produce temporary remissions in catatonic states, such as carbon dioxide (Loewenhardt, Lorenz, and Waters, 1929) or cocaine, are able to relieve this " bulbocapnine catatonia " (Buchman and Richter, 1931 ; Paterson and Richter, 1933). Kennedy (1939) has shown that convulsions have no effect in preventing the cataleptoid condition from appearing in the monkey, and that in the period following the convulsion the catalepsy is greatly increased. Guttiérrez-Noriega (1938), on the other hand, found that, with different doses of bulbocapnine in dogs, the catalepsy was improved after convulsions. The work of Quastel and Jowett (1939) on cerebral oxygen consumption during bulbocapnine intoxication makes it probable that any effects observed are due to a cumulative increase in the anoxia due to the convulsion. These findings are of interest in view of Friedman's (1937) observation that in camphorcardiazol therapy patients often showed profound catalepsy after their convulsions, as well as deep cyanosis. It would seem that a similar process is at work here, the camphor providing a prolonged state of lowered cerebral activity and the superadded convulsions bringing on catalepsy.

Effects of Convulsions on Metabolism

Studies of the effects of shock-therapy in this sphere are of especial interest, as it cannot be doubted that there is a profound effect on the metabolism of the central nervous system. Clinically it is evident that cerebral function is very sensitive to changes in oxygen tension such as are seen in anoxæmic states and at high altitudes, and also to alterations in the amount of available carbohydrates as in hypoglycæmia. It is just in this sensitivity to lack of oxygen and in its need for a continued supply of carbohydrate that the metabolism of brain-

tissue differs from that of other tissues. Wortis (1934) has furthermore demonstrated that the grey matter, especially of the cerebral and cerebellar cortices, has the greatest oxygen consumption, a fact which might be expected from the relative richness of their vascular supply.

The oxidation properties of the different kinds of brain-tissue can thus be interfered with by a gross lack of oxygen, by a deficiency of available carbohydrate or by a specific effect on the intermediate processes in cell oxidation, such as the intracellular enzymes which have been shown by Warburg to play an important part in making oxygen utilizable by the cells. Dameshek, Myerson, and Loman (1934) have shown that sodium amytal, which has such remarkable effects in procuring temporary remissions in catatonic stupor (Bleckwenn, 1931), causes a reduction in the utilization of oxygen and glucose by the brain. In understanding the effects of shock-therapy the experimental study of the metabolism of brain-tissue has been carried out (Wortis, 1935) mainly by three methods : first the Barcroft-Warburg technique, by which small amounts of living brain are kept under nearly physiological conditions and the oxygen consumption and carbon-dioxide elimination are measured ; secondly by the method of arterial and venous puncture, whereby the concentration of oxygen, glucose, and metabolites are compared in the blood entering and leaving the brain ; and thirdly by placing slices of brain in physiological solutions which support their nutrition, and determining by chemical analysis the amount of absorption of nutritive material and the production of the end-products of tissue metabolism.

Wortis (1933), using the Barcroft-Warburg technique, has shown that the respiratory quotient of brain-tissue in man and several animals is approximately unity, indicating that its nutrition is necessary to find out by which of these means brain-metabolism is altered or by what proportion of each. In insulin-therapy it is clear that the lack of available carbohydrate is likely to be the principal factor, but in convulsion-therapy the mechanism is less obvious. Wortis (1936) has shown that, in contrast to insulin, cardiazol causes no reduced oxidation in brain tissue removed immediately after the convulsion. It has also no effect on the metabolism of brain-slices immersed in physiological solutions.

Himwich and his co-workers (1938) studied the hæmoglobin saturation $\left(\text{i.e. } \frac{\text{oxygen content}}{\text{oxygen capacity}}\right)$ of blood from the femoral artery and jugular vein at different stages of the convulsion and have shown that towards the end this fell to 50 per cent., and concluded that convulsions cause a depression of cerebral function by decreasing the amount of oxygen available for the combustion of carbohydrate. There was no lowering of the blood-sugar in their cases, and Kerr and Antaki (1937) have also failed to demonstrate any reduction in carbohydrate content in the brain-tissue of animals after the convulsions.

There are a number of clinical similarities between the phenomena seen in anoxia and in shock-treatment. Fraser and Reitmann (1939) have observed the effects of causing patients to breathe very low concentrations (2 per cent.) of oxygen in nitrogen. The neurological phenomena bore no very marked

resemblance to those seen in induced convulsions, and, though unconsciousness and myoclonic movements were produced, there were no convulsions. This is in accord with the animal experiments of Armstrong and Heim (1938), who were unable to produce fits by anoxia, and of Simpson and Barker (1938), who subjected a number of epileptic patients to low concentrations of oxygen without inducing fits. Gellhorn (1938), from his animal experiments, however, concludes that anoxia is probably the principal factor in producing the effects of shock-therapy on the organism.

A good deal of work has been done on the general metabolism of patients during cardiazol treatment, especially on carbohydrate metabolism, on the *p*H of the blood and on the quantities of various substances in the blood, and some of these may throw some light on the effect of the drug. The theory of Georgi (1937), that the changes during a convulsion may be compared with the changes in the first phase of insulin-treatment, does not find much confirmation in the work of Maurer and his co-workers (1938), Harris (1938), and Walk and Mayer-Gross (1938). These workers have found little more than a simple rise of blood-sugar during the convulsion, which gradually subsides. Harris has also found no significant change in the form of the response to the ingestion of sugar before and after treatment. The fact that the majority of patients gain weight during treatment cannot be related entirely to carbohydrate metabolism, as increased appetite is usually a feature of the mental change. Harris has shown that this weight-increase has no relation to the occurrence of remissions.

Maurer and his co-workers (1938) have shown that, in the course of the convulsion, the *p*H of the blood may fall to the lowest levels compatible with life, but that there is no variation in cases where convulsions do not occur. It is to be presumed that the change is largely due to the enormous output of lactic acid which occurs as the result of the muscular effort of the convulsions. This change in *p*H is in exactly the opposite direction from that which occurs in insulin-therapy, although it may be followed by an over-compensating alkalosis which actually causes vomiting. This may be significant when it is recalled how difficult it is to cause any extensive change in *p*H in schizophrenics by the administration of alkalis (Golla, Mann, and Marsh, 1928).

These workers, and others (Bailey, Smith, and Moersch, 1938 ; Katzenelbogen, 1938), have also studied the changes in calcium and phosphorus content in the blood, and find that, while the former stays at a fairly constant level, the inorganic serum phosphorus is increased up to 100 per cent., presumably due to the replacement of the phosphate of the muscle-cell by lactate during the violent muscular contractions.

Neurological and Electroencephalographic Observations

Although it has been possible to induce fits in predisposed subjects for purposes of study by means of the hyperventilation method of Foerster and by electrical stimulation at operations, the clinical use of chemically induced convulsions has provided an opportunity of more accurate study of changes in function and metabolism during the convulsion itself. In most respects the

convulsions may be regarded as closely comparable with those of idiopathic epilepsy. The reflex changes, amnesia (Canseco, 1938), equivalents (Walk and Mayer-Gross, 1938), mode of recovery (Cohen, 1938), biochemical changes (Meduna, 1934), electrocardiographic changes (Gjessing, 1938 ; Erickson, 1939), and some of the pupil changes (Wespi, 1937 ; Birkmeyer, 1937) are all essentially similar. Nevertheless, the pattern of the cardiazol convulsion is very constant and has some special features of its own. The preliminary cough and sudden opening of the mouth, which so often produces dislocation of the jaw, are not seen in idiopathic epilepsy.

Study of the brain potentials during convulsion-therapy has yielded valuable information as to the mode of spread of the abnormal cortical activity, and has assisted in explaining this difference in convulsion-pattern. Cook and Grey Walter (1938) were the first to study the brain rhythms during the convulsion. They found that a few seconds after the injection abnormal waves appear in all areas, but that a few seconds later there is an increase in potential and a drop in frequency in an area which they localize in the superior frontal convolution. From this area the large slow waves spread over the rest of the cortex during the course of the convulsion. After this there is a period of comparatively little activity until normal rhythm returns. In essentials Rubin and Wall (1939) confirm these findings, though their localization of the starting-point from which the slow waves spread is less definite and rather nearer to the motor area. In the period following the convulsion, when the bipolar leads of Cook and Grey Walter recorded a relative inactivity, they, using monopolar recording, were able to detect disappearance of the slow waves until the record returned to normal.

These observations are comparable with those of Gibbs, Gibbs, and Lennox (1938) in idiopathic epilepsy, except that the origin of the discharge in these cases is not always from the same area. This possible localization of the starting-point of abnormal activity in the area 6 α β of Vogt, to which Foerster and others attribute an epileptogenic function, is clearly of the greatest interest.

In patients who have had an injection insufficient to cause a convulsion, but enough to cause a marked emotional response with restlessness and anxiety, Cook and Grey Walter found a period of generalized irregular cortical activity which persisted for some hours, and this, like the clinical state, disappeared at once if a true convulsion was induced by a second dose. Rubin and Wall have shown that the changes in cortical electrical activity can be correlated with the different stages of muscular activity demonstrated by high-speed motion-pictures and electromyograms by Strauss and Landis (1938), the first clonic stage, tonic stage, and second myoclonic stage each being accompanied by its characteristic electroencephalographic rhythm. They have also pointed out that the characteristic slow waves, which are seen only in the major convulsion, correspond to a drop in *p*H in the blood which also occurs only when an actual fit has taken place. This finding is of especial interest in view of the work of Dusser de Barenne, McCulloch, and Nims (1938), who have found that a reduction of *p*H in the cortex is accompanied by a reduction of amplitude and frequency in the potentials arising from it.

Patients whose electroencephalograms have been followed during a course of treatment do not usually show any significant change in the resting rhythms as the result of treatment, and Goodwin, Lloyd, and Hall (1938) have subjected rabbits to long series of convulsions without their having any marked effect on the form of the record or altering the course of the convulsive response. There is thus no evidence that the convulsion is able materially to alter the cortical rhythm or to introduce an abnormal one. MacMahon and Grey Walter's (1938) cases, on the other hand, suggest that an abnormal rhythm may be removed.

Some attempts have been made to compare the electroencephalographic records of schizophrenic and epileptic patients. Although no definite abnormality in the brain potentials has been found common to all schizophrenics, different abnormalities have been shown to occur in a fairly large proportion of cases. Jasper, Fitzpatrick, and Solomon (1938) could find no single specific form of activity which might distinguish patients diagnosed as schizophrenic from control groups. On the other hand, when making comparisons between schizophrenic and epileptic patients, they found that, while no definite contrast could be made out between the two groups to support the theory of biological antagonism (Meduna, 1934), there was a tendency for certain characteristics to predominate in each of the two groups. The cases diagnosed as schizophrenic and epileptic tended to fall at opposite ends of a scale based on the amount of brain potential activity of frequencies at or below the normal frequency of the alpha-rhythm. The schizophrenic group showed less of these slower waves. On the other hand, Gibbs, Gibbs, and Lennox have pointed out many electroencephalographic similarities between the two groups ; MacMahon and Grey Walter observed a true delta-wave discharge in three cases of schizophrenia and showed that this disappeared with clinical recovery, in one case spontaneously and in two cases after convulsion-therapy. It is useless to speculate too much at present on the significance of these findings, but they are certainly very striking.

Psychological Aspects of Convulsion-Therapy

The psychological effects of convulsions, as well as their effects on mental function, have aroused great interest not only on account of their bearing upon earlier work on the psychopathological significance of the convulsion in general, but because of the relation of this newer method of treatment to the psychotherapeutic approach. A fair number of observations are now available on the effects of the induced convulsion on the psyche, especially in relation to perception, memory, and emotional tone.

Schilder (1939) has studied the phenomena observed in the half-hour following the convulsion. He observes a marked difficulty in remembering the names of objects, a great tendency to perseveration and to paraphasia, and also difficulty in copying the gestalt patterns devised by Bender (1935), with a tendency to revert to primitive and archaic forms. These observations may be taken to indicate a profound organic disturbance of form-function.

In the affective sphere this period is characterized by emotional lability and overreaction and the formation of crude transferences. Cohen (1939) has studied the order in which function returns as the patient emerges from the convulsion, and finds that crude sensation appears first, followed by coarse sensory discrimination ; then the ability to focus attention on objects, followed by the ability to use them correctly. Memory is the last function to return, and, like other workers, Cohen finds that the amnesia becomes progressively delimited during the hours following the convulsion.

The memory defects associated with induced convulsions may be divided into two groups. The first of these is the retrograde amnesia in immediate association with the fit, which has been observed since the inception of the treatment. It may be regarded as in every way comparable to the amnesias associated with idiopathic epilepsy. Since it is the aim of the treatment to produce epileptiform convulsions, these amnesias are not to be regarded as an unfavourable effect, as they are an integral part of the convulsion. These immediate amnesias are said (Walk and Mayer-Gross, 1938) to be more marked with triazol 156 than with cardiazol.

The second group, that of memory disturbances persisting when the course of treatment is over, was not observed until much later. The condition has not, in fact, been studied over a sufficient period of time to establish whether it really is as temporary as would appear. Plattner (1938) was the first to notice that after " summation " therapy with insulin, Korsakoff-like memory disturbances, which usually disappeared after 4–8 weeks, were not uncommon. Weitbrecht (1938) also observed memory disorder after courses of cardiazol, but as some of these cases had had psychoses of long standing, he pointed out that it was difficult to be sure that the defect was not due to the effects of a prolonged psychosis rather than to the convulsions. He was inclined, also, to seek a psychopathological rather than a physical explanation for the amnesias.

In demonstrating minor lesions in the brains of dogs after convulsions, Reitmann (1938) drew attention to the memory disturbances observed in the human clinically. Two of these cases, who had difficulty in recalling addresses, names of friends, dates, and similar material, were published by Balta (1939). Tooth and Blackburn (1939) have also observed that nine out of 16 patients treated with convulsions had memory difficulties at the conclusion. Questioning of the relatives revealed that these patients had difficulty in remembering names and were very absent-minded. One patient who had learned shorthand in the months preceding her breakdown had great difficulty in remembering any of it after her psychosis had remitted, though she found it very easy to relearn. She was also frequently embarrassed by being unable to remember the names of friends, and when playing tennis often forgot the score. These disabilities ceased to be evident after six months. Another patient was noticed by her husband to be forgetful and careless in her housework, but after 8 months, apart from the fact that she had to use a shopping-list for even a small number of articles, there was no obvious disability.

These workers point out that this type of memory disorder is unlike that found in a dementing schizophrenic psychosis and resembles that seen after

epilepsy or concussion. They regard the changes as probably related to the minor pathological changes which, by analogy with animal experiments, presumably occur in the nervous system after convulsions. Just as it is difficult to prove that these changes are irreversible, so it is difficult to prove the contention of those (Berrington, Dynes, and Tooth and Blackburn) who hold that these reductions of mental efficiency, which certainly recover to a large extent at least, represent evidence of actual permanent mental deterioration. In an attempt to determine if this memory disorder is accompanied by a true deterioration, Tooth and Blackburn have applied the method of Babcock (1930) and shown that, in their cases, the ability with vocabulary tests was greater than with other tests which normally standardize at the same level, a fact which is taken to indicate deterioration. In comparing their findings in spontaneously remitting schizophrenics, in treated general paretics, epileptics, and convulsion-treated schizophrenics, they showed that there were close similarities between the post-convulsive and organic-deterioration groups. Although there has been some confirmation of Babcock's work (Wittmann, 1933 ; Gilbert, 1935), the validity of this or of any other test as an indication of irreversible mental deterioration is far from generally accepted.

It is very difficult to arrive at a satisfactory interpretation of the effects of induced convulsions on memory, as several factors may operate in their causation. The immediate amnesia for the fit and a period of time preceding and following it may be, as Schilder (1939) points out, perpetuated psychogenically to avoid recalling the unpleasant circumstances of the anxious period before the fit, but this does not seem to be a mechanism of great importance. The later memory disorders have some points in common with those seen in epileptics, such as the frequent difficulty in recalling names and detailed material. The way in which Tooth and Blackburn's patient forgot shorthand after convulsions, only to relearn it with great ease, is comparable to the " lernersparniss " phenomenon. On the other hand, there are similar disturbances found in other forms of cerebral pathology, such as vascular accidents, which clear up in a few months in exactly the same way. Although it is unlikely that after a series of convulsions which leave behind a considerable disturbance of memory there is no irreversible change in the nervous system, it seems unjustifiable, without more prolonged study of the case-material, to suggest that a process comparable to epileptic dementia occurs in these patients. Even with a picture strongly suggesting deterioration such as is seen in the cases reported by Dynes (1939), it is difficult, as Weitbrecht points out, to be sure how much is attributable to the convulsions and how much to the effects of a psychosis which, in these cases, was of over 3 years' duration.

It would seem that for evidence of deterioration it is at least as important to look for evidence of changes in personality and alterations in social relationships, but there is a paucity of observations on this point. There is certainly no record of the development of the antisocial traits associated with the chronic epileptic. Berrington (1939) is inclined to interpret the frequently noted lack of curiosity of the recovered patient about his illness, his lack of true insight into his former abnormal mental activity, and his increased preoccupation with

the simple processes of eating and living, to the exclusion of more imaginative and intellectual topics, as evidence of a deterioration of the higher mental functions.

In the affective sphere the disordered emotional responses of each post-convulsive period are accompanied by a series of changes in the attitude of the patient towards his attendants as the treatment progresses. In the early stages of remission emotional reactions of a primitive kind are manifest, either as the result of the sudden termination of a period of restricted affectivity or as the result of the shock effect of the treatment, and these subsequently become modified as the patient approaches normality. In three cases reported by Kennedy (1937) this process took place in a regular order, an excited and anxious phase being followed by an erotic-euphoric one with a strong positive transference, which gave way in turn to an attitude of reasonable co-operation.

The tendency to euphoria in the early stages of treatment was recognized from the first by Meduna, Lehmann-Facius, and others. There is no doubt that a very definite transference to the physician develops in a large proportion of cases. It is at first crude and infantile, but later more mature in form, and Schilder (1939) observes that this transference persists when treatment is over and can be used psychotherapeutically when the patient is being assisted to re-adapt himself to normal life. Dynes has drawn attention to the fact that, in cases which do not recover, the exaggerated mood-states and euphoric-hypomanic conditions provoked by the convulsions may persist for some time and cause difficulty in managing the patient.

Rees-Thomas and Wilson found that the nurses who were looking after patients who had convulsions thought that they had the effect of making the patient more accessible and communicative, and it is certain that their effect is to produce a state of increased co-operation which it is possible to exploit from the very beginning in the interests of their re-adaptation to normal life, by giving occupational therapy graduated according to the progress of the treatment. Ellery (1937) also comments on the use that can be made of the patient's new desire to communicate with those around him.

Many writers have spoken of the patient's attitude to the treatment and of the need of avoiding the fear of further injections which is sometimes aroused by their experience ; some of the methods of avoiding these unpleasant effects have already been discussed. Many of the patients who object to and fear the convulsions are unable to give very definite reasons for their objections, and it would seem that while the memory of the unpleasant feelings has been lost the affective reaction has stayed with the patient, and caused him to rationalize his refusal of treatment. Starks (1938), in comparing the subjective aspects of insulin and cardiazol therapies, observed that the majority of his convulsion patients found the treatment unpleasant, one quarter of them admitting to a fear of death in connection with the injections. Gillespie (1939) found that only three of 42 patients found treatment so unpleasant that they actively resisted it. He was able to obtain the accounts of the subjective sensations of 23 patients, the majority of whom found the treatment unpleasant in some way. He found a great variety of auræ preceding the fits, including feelings of unreality, flashes

of light, hallucinations of hearing, thoughts of a sexual nature, and pungent smells. Like other workers, he notes that a large proportion of the patients noticed unusual smells for some time after the convulsion.

This worker also improved our knowledge of the subjective aspect of this treatment by himself submitting to it. After an injection of 10 c.c. he felt his body turning, then " very rapidly something seemed to move in my arms and thorax and to pass up to the base of my neck, where it stopped and increased in intensity." He states the onset of unconsciousness was not unpleasant and felt like the onset of normal sleep. After the fit, " At first I could remember nothing of the morning's events, including the injection, and even the day before seemed indistinct." This amnesia wore off in the course of a day.

The explanation of the remissions which occur as the result of shock-treatment has provided a difficult problem to those who regard the schizophrenias as largely psychogenic in origin. The treatments had not long been in existence, however, before theories had been advanced to explain the improvement on psychoanalytic lines.

Jeliffe (1937) regarded the effects of insulin-shock as attributable to the fear of annihilation which causes less vital conflicts to be forgotten in the urgent need to adapt. Schilder (1939) believes that convulsion-therapy operates in a similar manner and refers to the previous studies of Clarke (1917), who claimed that psychologically the epileptic experiences death and rebirth in the fit. He regards the improvement and euphoria of the cardiazol patient as due to the elation and joy of rebirth, which allow him to build up his relations with other people anew. This concept of the struggle between life and death in shock-treatment had been previously discussed by Humbert and Friedemann (1937).

Schilder has commented on the nature of the insight found in recovered patients. He draws a distinction between the type usually found, in which the patient, in looking back on his past behaviour, realizes that by normal standards he has been behaving foolishly, and the dynamic insight of the patient who has come to understand and to leave behind his symptoms as the result of psychotherapy.

He feels that use should be made of the transference-situation set up by the treatment, to obtain this dynamic insight by means of psychotherapeutic talks with the patient when the course of convulsions has been completed.

It has been generally agreed at the conferences held on this subject that some sort of psychotherapeutic adjunct to the treatment is necessary, and, as Meduna has said, it has both a biochemical and a psychological aspect. It is at least necessary to allay the fears of the patient and to keep him employed with a graduated programme of occupational therapy until he is able to co-operate sufficiently to discuss his return to his former life. After this he must at least be regarded in the light of a convalescent who needs a little help and encouragement in taking over once more his full responsibilities.

Theoretical Aspects of Convulsion-Therapy

The theoretical basis which led to the first trial of the induced convulsion as a therapeutic agent was early recognized as at least not wholly explanatory of the changes produced, and there have been many attempts to rationalize the purely empirical use of the method which has followed. Although much of this theorization has been loose and ill-founded, some of the possibilities are worthy of mention. The suggestions involve psychological and humoral mechanisms as well as effects on the central nervous system.

Psychological.—The drastic nature of convulsion therapy has led to its being compared with the turntables, duckings, and floggings which were meted out to the mentally afflicted of earlier days. There have been many accounts of stuporose patients whose condition has remitted following a profound psychic shock and the beneficial effects of convulsions may be contributed to in this way. In the case of chronic catatonic patients the extra attention which they receive and the change in routine may also assist their recovery. If some schizophrenic states are to be regarded as withdrawal reactions from a difficult environment, the immediate necessity of adapting to the "assault on the person" (Meyer) provided by the convulsion, may cause a temporary suppression of less important issues and force return to normal contacts. The "death-threat" theory of Jeliffe (1937) and Schilder (1939) may be regarded as a psychoanalytic elaboration of this theme. One of the objections to this view is the fact that subconvulsant doses which produce powerful fears and affective reactions are less effective than convulsant doses, the effects of which leave far less impression on the patient.

Theories involving the Nervous System.—Stief, in his histological studies on animals after prolonged insulin-shock (Stief and Tokay, 1935), found, as had Schmid (1936), evidence of cerebral damage and cell-outfall. He considers (1938) that the insulin may have a selective action on diseased functional units and by this means eliminate those which are the cause of the mental state. In the case of convulsions he considers that instead of lack of glucose, anoxia brought about by vascular spasm is the intermediate mechanism. It is difficult to criticize this view as there is, as yet, insufficient evidence that early schizophrenia is related to abnormal function in some of the neurones.

The effects of convulsion-therapy have revived interest in the mechanism of the temporary remissions produced by carbon dioxide (Loewenhardt, Lorenz, and Waters, 1929), sodium amytal (Bleckwenn, 1934), and other depressant substances. These results have recently been reviewed by Berrington (1939). It seems possible that these substances have a depressant effect principally on the cortex and produce brief remissions during the period of their action, and that the late effects of convulsions and of hypoglycæmia may be an incomplete damage which depresses the same functions in a more permanent manner. If this were so, the remitted patient would be expected to be altered in some way, just as the emotional behaviour and motility are only approximately "normal" in the amytal remission. There is much support for the view that this is the case (Balta, 1938 ; Berrington, 1939 ; Dynes, 1939).

The electroencephalographic observations of Jasper, Fitzpatrick, and

Solomon (1938), who find in catatonics evidence of greater, rather than less, activity in the cortical potentials, is here of interest if it is supposed that in the process of remission an excessive abnormal functional activity is replaced by a reduced one of normal type.

It may be, however, that the changes which occur are not so much the result of structural changes but of alteration in the nature of the action of the functional units in the brain. Birkmeyer (1938), for instance, suggests that after the convulsions there may be a general depression of activity, which, when it is built up anew, becomes normal activity ; a similar view was taken by Angyal (1937) as to the mode of action of insulin-shock.

The question thus arises as to whether the patient secures his re-adaptation to normal life at the expense of a permanent lowering of functional efficiency. He may, in the language of chess, be sacrificing a piece to win the game. How much the patient is handicapped by these losses can only be found out by a careful comparison of his pre-psychotic personality and efficiency with his state when the illness and its treatment are over. From the point of view of social adjustment he seems to be little the worse.

Another possibility presents itself : since the activity of cerebral functional units is continuous whether the individual be active or stuporose, it may be supposed that conduction from one unit to another is occurring at all times, even though it does not result in thought or action. It might be compared to the ceaseless conduction of impulses by the muscle of the auricle. If, in schizophrenic states, this continuous activity becomes abnormal in type so as to produce a disorder of conduct, just as the abnormal conduction of auricular fibrillation produces abnormal ventricular behaviour, it may be that a temporary gross lowering of activity acts in restarting the normal rhythm of activity in a way comparable to that in which quinidine restores normal cardiac rhythm. This comparison is capable of very extensive but as yet quite unjustifiable elaboration.

While there is evidence (Hall and Goodwin, 1938 ; Himwich *et al.*, 1939) that there is a severe anoxæmia at the time of the convulsion, and that the histological changes observed may be due to this cause, it is possible that other vascular mechanisms may play a part. Gellhorn (1938) regards cerebral anoxia as the common intermediate mechanism in all forms of shock-therapy, but he suggests that its beneficial effects on schizophrenic states are due not to a depressant action on the cerebrum but to reflex stimulation of the sympathetic system.

The hearts and vessels of chronic catatonics are frequently found at autopsy to be small and hypoplastic (Lewis, 1936) and marked vascular stasis is often present in this condition. It is notable that after a few convulsions this stasis clears up, and it seems possible that the convulsion, by increasing the use of the capillary field in the brain and elsewhere, can restore the normal blood supply to these parts. This view receives support also from the work of Freeman (1934), who has demonstrated a considerable slowing of the circulation-time in schizophrenics, although others have been unable to confirm this (Finesinger, Cohen, and Thompson, 1938 ; Loewenhardt, Lorenz, Martin, and Malone,

1929). Angyal believes that by increasing the bloodflow in this way the brain is flushed of toxic material.

Antagonism between Schizophrenia and Epilepsy.—Although, as has been described, convulsion-therapy was founded on the observation that schizophrenics sometimes improve after the appearance of convulsions, the presence of an actual antagonism between the two conditions is far from proved. Although the work of Glaus (1931) and of Steiner and Strauss (1932), which includes observations of 12,000 cases, would suggest that epileptiform fits are of much rarer occurrence in schizophrenics than would be expected from the general incidence of the two conditions, Esser has collected observations on about 10,000 from the literature, and finds that convulsions are fairly frequent in cases of catatonia and are by no means always followed by a remission of symptoms. The subject has been reviewed frequently during recent years, and it is certainly not possible to show that the conditions are almost mutually exclusive, as was at first thought. There seems to be little support for the theory of antagonism when metabolic comparisons are made between the two conditions, but the observations of Jasper, Fitzpatrick, and Solomon on the electrical changes in the cortex (referred to above) show that in this respect there are some points of contrast. The favourable effects of convulsions in many cases of manic-depressive psychosis cannot, of course, be explained by this hypothesis, and v. Meduna himself is now inclined to agree with his critics. " The criticism . . . seems to be justified as much by the results of convulsion-therapy in non-schizophrenic conditions, especially melancholia " (Meduna and Rohny, 1939).

Summary and General Impressions

There can be no doubt that the introduction of pharmacological shock-therapy has been the most stimulating event in the therapy of mental disorders since the discovery of the malarial treatment of general paralysis. It will be recalled how high recovery rates were recorded in the early reports on malarial therapy, and how it came to be shown that these results could only be expected when the condition had been diagnosed early, and too much permanent damage had not already been done. It will be recalled also how, when the use of this method was extended to other mental disorders, although some favourable results were recorded at first, it soon became clear that the treatment was specific for one disease. There are some similarities in the present situation with convulsion-therapy. Not only have later results shown that the early high recovery rates cannot be uniformly anticipated, but it is evident that very little can be expected when the pathological process has advanced beyond a certain point. Further, the recovery rates in some series are lower than the spontaneous remission rate in some prognostically favourable groups of schizophrenics, and this, with the high frequency of relapse, calls into question the actual usefulness of this mode of treatment. Extension of the method to other forms of mental disorder, especially manic-depressive psychosis and degenerative hysteria, has been attended with some success, and it seems

probable that, as with prolonged narcosis, convulsion-therapy may be able to determine a change in the individual's reaction in cases where such a change might be expected to occur in any case.

In assessing the value of convulsion-therapy we have to face two new difficulties. First : we have but little knowledge of the pathology of the conditions which appear to benefit by it, nor do we know whether the conditions which exhibit the schizophrenic symptom-complexes have a common pathology ; and secondly : we have no exact idea of the mode of action of convulsions and cannot, therefore, know at what cost to the individual the improvement is obtained. We are aware that a normal man may have malaria without subsequent deterioration of his mental health and efficiency, but we know that individuals who have spontaneous convulsions, with many points of similarity with cardiazol convulsions, do tend to deteriorate, frequently very rapidly, and that this deterioration is associated with abnormalities of memory and psychomotor and affective changes such as have been described after therapeutic convulsions.

Before undertaking treatment, therefore, we must realize that, if we are to return to normal life a person who, by reason of an apparently deteriorating mental disorder, may not be able to adapt himself to society again, we may be doing so at the price of damaging some of the more highly developed parts of his nervous system. Even, however, if it were certain that permanent damage to the nervous system were inevitable, it might still be justifiable to continue.

Many cases of general paralysis who have recovered as the result of pyrexial treatment have brains that have been severely damaged by the disease before treatment was commenced, and yet are seemingly able to adapt themselves even better than before their illness, possibly because the illness has removed an inhibiting self-criticism which formerly prevented them from taking chances with their environment. It is by no means certain that the retention of the highest intellectual functions is consistent with the optimum adaptation to society or with the greatest happiness.

The effects of convulsion-therapy have done much to stimulate speculation and experiment, and have provided a link with the earlier work on temporary remissions. They have given renewed confidence to those who hold that some at least of the schizophrenic reactions may be reversible if they are appropriately treated before permanent change has occurred.

It is unlikely that one mode of action alone is able to bring about the beneficial effects in all cases. It is at least likely that there are psychical and somatic components in the mechanism of recovery, a mechanism which may vary in cases of different kinds within the schizophrenic group. If in future convulsion-therapy has a more limited application than was at first thought, this is no reason for its total abandonment. It is our duty to develop, as early as possible, a sense of proportion with regard to the method and to find its true place in psychiatric treatment.

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Cerebral Vasomotor Regulation.—A method for the determination of the cerebral control of the peripheral circulation in man is described. In two cases with localized cortical lesions the cerebral control of the circulation in the hands was affected. (B. McA.)

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*Partial Thenar Atrophy : a Clinical Entity. R. Wartenberg. 373.

*Experimental Study of Pathogenesis of Cerebral Changes following Prolonged Insulin Hypoglycemia. H. Yannet and J. F. Iannucci. 395.

*Recovery of Sympathetic Nerve Function in Skin Transplants. F. E. Kredel and D. B. Phemister. 403.

*Palatal Myoclonus. O. Sittig and V. Haskovec. 413.

*Effect of Pleasant and of Unpleasant Ideas on Respiration in Psychoneurotic Patients. J. E. Finesinger. 425.

*Protective Effect of Cholesterol in Experimental Epilepsy. R. B. Aird and C. Gurchot. 491.

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An Unusual Form of Lymphocytic Choriomeningitis. J. E. Skogland and A. B. Baker. 507.

Convulsive and Other Neurologic Phenomena appearing in Senile and Arteriosclerotic Psychoses. J. B. Tompkins. 513.

Special Articles.

Objective Technics in Personality Testing. G. C. Booth. 514.

Partial Thenar Atrophy.—Partial thenar atrophy is a definite clinical entity with the following characteristics : atrophy of the muscles on the outer radial aspect of the thenar eminence, of slow, chronic, and hardly noticeable development and with a marked tendency to become stationary. There are no fibrillary twitchings, no tenderness of nerve trunks, no sensory changes, and no other motor disturbances. Paræsthesias without, or less commonly with, pain are often present on both hands ; these usually precede the appearance of the atrophy. An attempt has been made to explain this "partial thenar atrophy," which may be regarded as a clinical entity, on the basis of toxico-traumatic damage of the corresponding branches of the median nerves. The presence of a toxic influence on these nerves is indicated by the paræthesias, which may be considered as an expression of chronic sensory polyneuritis due to an undetermined endotoxic or exotoxic process. The traumatic factor is supplied by the fact that in some persons the branches of the median nerve to the muscles of the thenar eminence may have an abnormal course in relation to the ligamentum carpi transversum, and this be subjected to abnormal pressure, stretching, or strangulation in ordinary use of the hand. These two factors would need to coincide in order to produce the partial thenar atrophy, and this would account for the relative rarity of the condition. The second possible explanation, which seems to be more con-

vincing, is based on the assumption that the muscles involved, because they are phylogenetically young structures, may be congenitally inferior and therefore may become abiotrophic and degenerate during the course of life. This degeneration may take place spontaneously, but it may also be precipitated by added external damage, such as the pathological condition that underlies the acroparæsthesias. (R. M. S.)

Pathogenesis of Cerebral Changes following Insulin.—The present study is an investigation of some factors considered responsible for the production of cerebral injury following prolonged insulin hypoglycæmia. The mechanism for the cerebral damage was not found to be casually related to changes in oxygen saturation of arterial blood or to the presence of marked circulatory impairment. It was found that relatively small doses of insulin, i.e. 3 units per kilogram, resulted in prolonged hypoglycæmia but did not produce cerebral injury. However, larger doses, i.e. from 15 to 20 units per kilogram, did result in widespread cerebral damage, although the hypoglycæmia produced was neither more prolonged nor more severe as judged by the concentrations of the blood sugar. These results were interpreted as suggesting that the injurious effects of large doses of insulin are brought about by the promotion of some reaction in the cerebral cells which is relatively harmless if the blood sugar is maintained. Animals under anæsthesia induced by pentobarbital sodium were found to be more susceptible to the toxic action of insulin. (R. M. S.)

Sympathetic Nerve Function in Skin Transplants.—Recovery of sympathetic function is described in a series of pedicle skin flaps in man. Sudomotor, vasomotor, pilomotor, and sebomotor functions may recover. The amount of restoration parallels to some extent the recovery of cutaneous sensation. Return of pilomotor function and regeneration of sympathetic fibres occur in the peripherally denervated skin of the cat. (R. M. S.)

Palatal Myoclonus.—In a case of palatal myoclonus anatomical study revealed a lesion in the right cerebellar hemisphere, the dentate nucleus, and the adjacent white matter : pseudohypertrophy of the left olivary body : degeneration of the right restiform body and the right superior cerebellar peduncle, and atrophy of the left red nucleus. (R. M. S.)

Effect of Ideas on Respiration.—A lengthy paper devoted to a comprehensive study of various aspects of the respiratory function in psychoneurotic patients. (R. M. S.)

Cholesterol in Experimental Epilepsy.—The results of this study were interpreted as consistent with the theory that the vital lipoids play a significant role in the permeability of cell membranes, and through this mechanism are an important factor in epilepsy. (R. M. S.)

Vol. 42. No. 4. October 1939.

*Pathologic Laughing and Crying. C. Davison and H. Kelman. 595.
*Treatment of Schizophrenia with Glandular Extracts. S. Fischer. 644.
*Capillary Structure in Patients with Schizophrenia. D. M. Olkon. 652.
*Lesions of the Fundus associated with Brain Hemorrhage. L. L. Tureen. 664.
*Cerebral Changes in Fatal Cases following Treatment with Barbital, Soluble Barbital, U.S.P., Insulin, and Metrazol. G. B. Hassin. 679.
Histopathologic Changes in the Brain following Experimental Injections of Metrazol. E. Liebert and A. Weil. 690.
*Mode of Action of Brilliant Vital Red in Epilepsy. R. B. Aird. 700.
*Skin and Body Temperatures of Schizophrenic and Normal Subjects under varying Environmental Conditions. H. Freeman. 724.

Case Reports.

The Central Visual System : Evidence against Bilateral Representation through the Splenium of the Corpus Callosum. O. R. Hyndman. 735.

Pathologic Laughing and Crying.—From an analysis of more than 50 cases, together with a study of clinicopathological material and animal experiments reported in the literature, the writers have attempted to reconstruct the centres and pathways regulating laughing and crying. The cases of cortical lesions indicate that certain cortical areas, namely, the frontal, premotor, motor, parietal, temporal, and hippocampal, may act as centres for integration of these affective responses. These impulses are mediated by pathways which are in intimate connection with the hypothalamus. The hypothalamus or some other of the diencephalic nuclei, which are under cortical inhibitory influence, are the main centres or stations for the release of affective responses. A lesion of the corticohypothalamic tract removes cortical control, thereby inducing excessive affective responses. The secondary involvement of the thalamic nuclei, striatum, and pallidum in many of the clinicopathological cases and the œdema of these structures in the experimental animal suggest that these areas may also act as centres for the production of these affective responses and that, by means of pathways, they are in intimate association with the hypothalamus. The group of cases of selective lesions of the mesencephalon and metencephalon and the animal experiments indicate that there are pathways, and possibly independent centres in these regions for the production of laughing and crying. Some of these pathways are in intimate connection with the hypothalamus and the faciorespiratory nuclei. (R. M. S.)

Schizophrenia and Glandular Extracts.—The author states that treatment of schizophrenic patients with an extract containing anterior pituitary-like substances from the urine of pregnant women produces good therapeutic results. As complete remission was obtained in 63·4 per cent. and improvement in 21·5 per cent., this claim would appear to err on the side of modesty. (R. M. S.)

Capillary Structure in Schizophrenics.—In patients with schizophrenia the cutaneous capillaries showed striking deviations from the normal, the severity of this disease being related to the degree of derangement of the capillary structure. The studies suggest that schizophrenia falls in the category of vegetative and metabolic disorders. (R. M. S.)

Lesions of Fundus and Brain Hæmorrhage.—The ocular fundi in 23 cases of massive hæmorrhage of the brain were examined, in seven on a number of occasions, over a period of hours or days. Swelling of the optic disc was found in association most often with intraventricular hæmorrhage, which was not accompanied by a subarachnoid or pontile hæmorrhage. Retinal hæmorrhages were not found to be characteristically associated with retinal arteriosclerosis, but occurred in the course of subarachnoid and pontile hæmorrhage. The appearance of papillœdema and retinal hæmorrhages in cases of cerebral hæmorrhage leads on occasion to difficulties in differentiation from tumour of the brain. (R. M. S.)

Cerebral Changes following Barbital Treatment.—Barbiturates, insulin, and metrazol produce morphological changes in the ganglion cells of the brain, often associated with neuronophagia, but without marked macroglial or microglial reactive phenomena. The changes are diffuse and appear to be somewhat more marked in the medulla, especially the olivary bodies. Distention of the subarachnoid space and the cerebral tissue spaces—œdema—is a dangerous occurrence and is much more significant than the changes in the ganglion cells. The changes in the ganglion cells are not specific, for they are the same regardless of the type of poison; they also resemble changes produced experimentally by injections of a variety of organic or inorganic poisons. (R. M. S.)

Brilliant Vital Red and Epilepsy.—Brilliant vital red affords protection in cases of human epilepsy. This fact, in addition to various other considerations which are discussed, affords strong evidence in support of the hypothesis that "convulsive toxins" and the endothelium of the hæmoencephalitic barrier are factors of ætiological importance in human epilepsy and that the relation between them is analagous to that demonstrated in experimental epilepsy. (R. M. S.)

Skin and Body Temperatures of Schizophrenics.—Schizophrenic and normal subjects were exposed to varying environmental conditions, in the nude and under fasting conditions. Skin and rectal temperatures were measured by means of thermocouples. It was found that immediately after exposure the schizophrenic patients tended to have warmer extremities than the normal subjects. Exposure to cold conditions (15°, 20°, and 24° C.: 59°, 68°, and 75·2 F.) resulted consistently in greater cooling of the skin in the patients than in the normal controls. Exposure to hot conditions (44° C.: 110·2° F.) resulted in no difference in the response of normal and of schizophrenic subjects. Exposure to high humidity at low and high temperatures showed no difference between the patients and the normal subjects. The rectal temperatures of schizophrenic and normal subjects reacted similarly under all conditions. (R. M. S.)

Vol. 42. No. 5. November 1939.

*Involvement of the Nervous System associated with Endocarditis: Neuropsychiatric and Neuropathologic Observations in Forty-Two Cases of Fatal Outcome. J. W. Kernohan, H. W. Woltman, and A. R. Barnes. 789.
*Subdural Shadows in Pneumoencephalograms: their Diagnosis, Origin, and Significance. T. J. C. von Storch and A. Buermann. 810.
*Effect of Epinephrine on Convulsions. E. Gellhorn, C. W. Darrow, and L. Yesinick. 826.
Role of Allergy in Multiple Sclerosis: Incidence of Atopy in a Series of Forty Cases. R. L. Baer and M. B. Sulzberger. 837.
Gross Pathology of the Oligodendrogliomas. K. Lowenberg and R. W. Waggoner. 842.
*Rhythmic Variation of Respiratory Excursion with Bilateral Injury of Cortical Efferent Fibers. R. V. Grimmer, F. H. Hesser, and O. R. Langworthy. 862.
*The Human Pyramidal Tract: a Fiber and Numerical Analysis. A. M. Lassek and G. L. Rasmussen. 872.
Follow-up Study of Five Hundred Patients with Schizophrenia admitted to the Hospital from 1913 to 1923. T. A. C. Rennie and J. B. Fowler. 877.

Case Reports.
Pinealoma of Diffuse Ependymal Origin. R. P. Mackay. 892.
Hemorrhages into the Central Nervous System following Lumbar Spinal Puncture. S. Androp. 903.

Technical Notes.
A Classroom Outline for the Pathologic Diagnosis of Primary Intracranial Neoplasms: Six Differential Characteristics. L. Alexander. 912.

Involvement of Nervous System with Endocarditis.—Pathological studies of the central nervous system have disclosed beyond question that changes in the central nervous system, with or without associated clinical symptoms, are not only common to all types of endocarditis but also are as distinctive as are the various types of endocarditis and that they may be correlated

one with the other. It must be clear that more careful neurological and psychiatric surveys of patients who have endocarditis would augment information and probably would indicate a greater incidence of such symptoms than is now appreciated. (R. M. S.)

Subdural Shadows in Pneumoencephalograms.—The writers discuss the significance of the presence of gas in the subdural space after and during lumbar pneumoencephalography. A gas may enter the intracranial subdural space during lumbar encephalographic examination (*a*) by direct introduction into the lumbar subdural space or (*b*) through tears in the arachnoid which have occurred before, during, or after the examination. Air or its constituent gases cannot be made to pass through the human arachnoid at a pressure of 450 mm. of water (0·627 lb. per sq. in.) maintained *in vitro* for 72 hours. It is unlikely that these gases pass through an intact arachnoid *in vivo* as a result of the encephalographic procedure. The presence of subdural air in an encephalogram, when not introduced by way of the lumbar subdural space, implies that the arachnoid has been torn and suggests that the membrane has been involved in a superficial pathological process. Subdural gas occurs most frequently in patients who have been subjected to cranial injuries. Although often associated with cranial injury, and occasionally with subdural hæmatomas, subdural gas is diagnostic of neither. (R. M. S.)

Epinephrine and Convulsions.—Experiments on narcotized cats show that the anticonvulsant action of epinephrine is linked with carotid sinus and depressor reflexes. The action is abolished by bilateral vagotomy and denervation of both carotid sinuses, but is still present after carotid sinus denervation if one vagus nerve is intact. These facts and the observation that convulsions are frequently increased when the blood pressure is lowered by amyl nitrite make it probable that pressor reflexes from the carotid sinus and arch of the aorta regulate the excitability of the somatic nervous system in a manner similar to that shown by Darrow and Gellhorn for the autonomic system. (R. M. S.)

Respiratory Rhythmic Variation with Injury of Cortical Fibres.—The authors' cases are compared with cases of non-neurological conditions in which rhythmicity of respiratory excursion is shown. The general mechanism of periodic breathing is considered and the method of cerebral control of respiration discussed. (R. M. S.)

Human Pyramidal Tract.—The predominant type of fibre in the human pyramidal tract is one of small calibre. Numerically, large fibres are scarce. Neither small or large fibres are aggregated in any one region of the pyramidal tract, but are equally dispersed throughout. Slightly over 1,000,000 pyramidal tract fibres enter the spinal cord on one side. It is believed that cells other than those of the Betz type give origin to a large percentage of pyramidal tract fibres and that these cells, wherever they may be located, are small. The pyramidal tract, because of the preponderance of small fibres, should, on the whole, be a bundle which conducts slowly. (R. M. S.)

ARCHIVOS ARGENTINOS DE NEUROLOGIA

Vol. 20. Nos. 5–6. May and June 1939.

El Electroencefalograma Humano. Sus aplicaciones a la Fisiologia y Patologia Cerebrales. (The electroencephalogram. Its application to physiology and cerebral pathology.) M. Balado, L. F. Romero, and P. J. Noiseux. 215.

Vol. 21. Nos. 1–2. July–August 1939.

Valor Diagnóstico Quirúrgico dei Electroencefalograma. (The surgical diagnostic value of the electroencephalogram.) J. C. Christensen. 5.

Ruptura de Vejiga en Dementes Paraliticos. (Rupture of arteries in dementia paralytica.) J. Irazu. 30.

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Vol. 62. No. 3. September 1939.

Acute and Subacute Necrotic Myelitis. J. G. Greenfield and J. W. Aldren Turner. 227.

Some Observations on Central Pain. D. Kendall. 253.

The Venous Drainage of the Brain, with Special Reference to the Galenic System. B. Schlesinger. 274.

Neurological Sequelæ of "Kernicterus." G. M. Fitzgerald, J. G. Greenfield, and B. Kounine. 292.

False Diverticulum of a Lateral Ventricle causing Hemiplegia in Chronic Internal Hydrocephalus. D. W. C. Northfield and D. S. Russell. 311.

*The Abnormal Cortical Potentials associated with High Intracranial Pressure. D. Williams. 321.

Cortical Potentials and High Intracranial Pressure.—Characteristic changes are seen in the electrical potentials recorded from patients with high intracranial pressure. There is little correlation between these changes and the height of the pressure or its clinical effects. Experimental evidence is advanced to show that the abnormal slow waves are due to secondary osmotic changes resulting in œdema of the white matter. These changes may determine the alteration in consciousness found in such cases. (D. J. W.)

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Vol. 34 (1). No. 4. April 1939.

Crimes en État de Confusion Mentale. (Crimes in relation to a state of mental confusion.) E. Leroy and P. Masquin. 169.

Réflexions sur la Valeur Scientifique et Morale de la Psychanalyse. (The moral and scientific value of psychoanalysis.) H. Ey. 189.

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Vol. 73. No. 4. July 1939.

*An Experimental Investigation of the Motor Cortex and Pyramidal Tract of *Echidna Aculeata*. F. Goldby. 509.

*A Specific Factor in Extracts of the Choroid Plexus influencing the Permeability of the Myelencephalic Roof. H. Cohen and S. Daines. 525.

*Partial Degeneration of the Nerve Supply of the Adrenal. A Study in Autonomic Innervation. J. Z. Young. 540.

*An Experimental Investigation of the Nerve Supply to the Adrenal Medulla of the Cat. W. d'A. Maycock and T. S. Heslop. 551.

*Discontinuity in the Nervous System of Cœlenterates. H. H. Woollard (the late) and J. A. Harpman. 559.

*Structural Changes in the Isolated Visual Cortex. W. E. Le Gros Clark and S. Sunderland. 563.

Motor Cortex and Pyramidal Tract of Echidna Aculeata.—A description has been given of the results of the electrical stimulation of the cortex of a number of specimens of *Echidna aculeata*. The results in the main confirm Abbie (1938). An excitable area far back between the sulci α and β is present. In it movements of the tail, hindlimb, trunk, forelimb, and head and neck are represented in that order, from above downwards. The threshold for effective stimulation is of the same order of magnitude as for the motor cortex of other mammals. Destruction of the upper part of this area leads to degeneration in a long cortical spinal tract which has been demonstrated by the Marchi method. The tract runs through the cerebral peduncle, decussates in the pons, and continues in the " Nonalbündel " of Kölliker, superficial to the spinal root of the trigeminal nerve throughout the medulla. It enters the most posterior part of the lateral column of the spinal cord and has been traced caudally as the 24th spinal segment. No evidence was found for the presence of a pyramidal tract close to the mid-ventral line of the medulla, nor for a decussation in the usual position at the caudal end of the medulla. Degeneration in intrinsic fibres of the forebrain resulting from the same lesion is also described. It affects association fibres, the anterior commissure, cortico-thalamic connections, the alveus and forming systems, but brings to light no new facts of importance. (A. G. M. W.)

Influence of Choroid Plexus on Permeability of Myelencephalic Roof.—Extract of choroid plexus contains a factor which has the power of increasing tissue permeability. A similar property is shown by extract of meninges but in much less degree, while it is entirely lacking in extract of brain tissue. The factor present in choroid plexus extract is species specific in its influence on tissue permeability. Experimental evidence is recorded suggesting that the factor elaborated by the choroid plexus plays an important part in the mechanism underlying the first extraventricular escape of fluid from the embryonic central nervous system, and it is suggested that it exerts its influence by increasing the permeability of the membrane areas in the myelencephalic roof, thus permitting the extraneural escape of intraventricular fluid. (A. G. M. W.)

Partial Degeneration of Nerve Supply of Adrenal.—Section of spinal roots in the cat is followed by disappearance of the nerve fibres which innervate the chromaffin cells of the adrenal medulla of the same side. This confirms the findings of Elliot, Hollinshead, and Swinyard that the innervation of the chromaffin tissue is preganglionic. The segments over which the adrenal fibres leave the cord are D6–D16 (L3), with possibly a few fibres from higher and lower segments in some cases. By section of this whole series of roots on one side total denervation of the ipsilateral medulla can be achieved. No evidence of contralateral innervation was found. Section of some only of these roots results in the production of local areas of degeneration in the medulla. Segmental relations are preserved, the front end of the gland receiving fibres from the more anterior roots. The separate fibres do not constitute an anastomosing plexus, but each innervates a defined area of the

gland. Section of the great splanchnic nerve produces denervation of the anterior half of the medulla. The lesser splanchnics contain most of the rest of the fibres, but a few run through lower sympathetic ganglia. Total denervation of the gland can therefore be assured by cutting the great splanchnics and removing the sympathetic chain from the diaphragm to the ganglion which gives a transverse ramus to D17 (L4). (A. G. M. W.)

Nerve Supply to Adrenal Medulla.—The distribution and relative importance of the adreno-secretory nerves of the adrenal medulla have been investigated in the cat, using the retraction of the denervated nictitating membrane as an indicator of the adrenaline release by nerve stimulation. The nerve supply of the adrenal medulla is derived from the ipsilateral thoracico-lumbar sympathetic outflow. Most of the adreno-secretory nerves are carried in the greater and lesser splanchnic nerves. Some also run to the adrenal medulla from the first and second lumbar sympathetic ganglia. The relative importance of these paths varies from animal to animal. Occasionally adreno-secretory nerves may enter the lumbar sympathetic chains at the third lumbar ganglia and ascend to the second lumbar ganglia, whence they pass to the adrenal glands. No release was obtained by stimulation of the vagus nerves. (A. G. M. W.)

Discontinuity in Nervous System of Cœlenterates.—The histology of the nervous system in the sea-anemones *Tealia felina* and *Actinia equina* and the jelly-fishes *Cyanea lamarcki* and *Chrysaora isosceles*, studied by the methods of methylene blue and gold chloride, is described. It is concluded that the nervous system in these cœlenterates consists of nerve cells the processes of which are discontinuous. The nerve fibres frequently intertwine but never fuse. Nerve fibres terminate on muscle cells by small expansions. (A. G. M. W.)

Structural Changes in Isolated Visual Cortex.—The structure of an isolated area of visual cortex shows relatively little change in its cell or fibre architecture. This is taken to indicate the richness of the intra-cortical connection of each part of the cortex with the immediately neighbouring cortex. In the isolated cortex there is a slight general reduction of cells which affect all the laminæ. Most of the large stellate cells of lamina IV*b* and many of the large solitary cells of Meynert in lamina VI undergo atrophy and disappear. Evidence is adduced that these cells give origin to projection fibres passing to subcortical centres rather than to association fibres either to neighbouring or distant areas of cortex. In the isolated cortex there is a reduction of the number of individual radial fibres, while the number of fasciculi which they compose remains unchanged. It is probable that these radial fibres are association fibres derived from other parts of the visual cortex. The network of obliquely disposed fibres in the deeper levels of the cortex mostly disappears : the experiments suggest that these fibres are projection fibres derived from subcortical centres. The stria of Gennari remains apparently unchanged in width and density. (A. G. M. W.)

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*Some Observations on the Morphology of the Synapse in the Cat's Spinal Cord. M. L. Barr. 1.
*An Experimental Investigation of the Motor Cortex and its Connexions in the Phalanger, *Trichosurus Vulpecula*. F. Goldby. 12.
Experiments on the Development of the Amphibian *Mesonephros*. R. J. O'Connor. 34.
*Some Observations on the Lymphatics of the Nasal Mucous Membrane in the Cat and Monkey. J. M. Yoffey and C. K. Drinker. 45.
*The Innervation of the Gum of *Talpa Europea*. W. Lewinsky and D. Stewart. 53.
The Cervical Region of the Lacertilia. A Critical Review of Certain Aspects of Its Anatomy. W. E. Adams. 57.
The Occurrence of the Lemurine Form of the Ectotympanic in a Primitive Marsupial. F. Wood Jones and V. F. Lambert. 72.
The Structure of the Epiphysis in *Sphenodon* and the Primitive Form of Secondary Centre. R. W. Haines. 80.
*The Cell Structures of the Mamillary Body in the Mammals and in Man. J. Rose. 91.
Anastomosis between the Rectal and Uterine Veins forming a Connexion between the Somatic and Portal Venous System in the Recto-Uterine Pouch. E. G. Wermuth. 116.

Morphology of Synapse in Cat's Spinal Cord.—The morphology of the synapse was studied in Cajal reduced silver nitrate preparations of normal spinal cords from 30 mature cats. Modification 4 of Cajal's technique, involving formalin fixation, was found most generally useful. In cells of the ventral horn and the chief portion of the dorsal horn axon terminations as end-bulbs are distributed fairly uniformly over the surface of the cell body and the proximal portion of the dendrites. End-bulbs appear to be less numerous on the distal portions of the dendrites. The density of end-bulbs numerically on the neurone is essentially the same in cells of the ventral horn and chief portion of the dorsal horn and in the various segments of the spinal cord. The density of end-bulbs on the surface of the cell body of a ventral horn cell is of the order of sixteen end-bulbs per 100 sq. μ by the technique employed. There are several thousand end-bulbs on a single larger motor neurone of the spinal cord in the cat. Approximately 38 per cent. of the cell membrane is devoted to the formation of synaptic junctions with other neurones. Considerable variation exists in the size, shape, and staining affinities of individual end-bulbs. The size may vary from less than 1·0 μ in diameter to 4·0 μ

by 5·0 μ. End-bulbs vary in shape from round to spatulate. The most typical feature of their internal structure is a fine fibril extending the length of the end-bulb appearing as a continuation of the parent nerve fibre. The smaller end-bulbs predominate on cells of the lateral groups of the ventral horn. End-bulbs of intermediate and larger sizes predominate on cells of the medial groups of the ventral horn and the chief portion of the dorsal horn of grey matter. (A. G. M. W.)

Motor Cortex and Connections in Trichosurus Vulpecula.—An electrically excitable area has been found in the cortex of the anterior third of the hemisphere in the phalanger, *Trichosurus vulpecula*. It falls short of the frontal pole, which is inexcitable, by about 3 mm. In it movements of the head and neck, forelimb, possibly trunk, and certainly hindlimb, are represented. The threshold for effective stimulation is similar to that for the motor cortex of other mammals. The area defined by stimulation corresponds with a cytoarchitectonic area, but is rather larger. The latter shows most of the characteristics of Brodmann's Area 4, but lamina IV, usually absent in this area, is present although not typically granular. Destruction of the motor area leads only to transient motor disabilities in the hetero-lateral limbs. Marchi experiments have shown that a cortico-spinal tract arises within the anterior third of the hemisphere, probably from the motor area, and after a complete decussation at the hind end of the medulla extends in the posterior column at least as far as the mid-thoracic segments of the spinal cord. They suggest that cortico-thalamic fibres from this part of the hemisphere are similar to those in placental mammals, but that fronto-pontine fibres are scanty or non-myelinated. The Marchi results, so far as they concern the cortico-spinal tracts, have been checked by experiments in which 12 weeks were allowed for degeneration, after which parts of the nervous system were stained by the Davenport silver method. Many cortico-spinal fibres are found to be non-myelinated. In comparison with *Didelphys virginiana*, the chief difference lies in the greater length of the cortico-spinal tract and in the representation of hindlimb movements in the cortex in the phalanger. (A. G. M. W.)

Lymphatics of Nasal Mucous Membrane.—In the nose and pharynx of the cat and monkey there is a rich lymphatic plexus which drains into the deep cervical lymph duct. The vessels of this plexus are in very close contact with the nasopharyngeal epithelium. The plexus may readily be injected from the cranial subarachnoid space with India ink or a solution of potassium ferrocyanide and iron ammonium citrate. (A. G. M. W.)

Innervation of Gum of Talpa Europea.—The gum of the mole has a much richer nerve-supply than the human. The nerves show three types of ending: free endings, end swellings, and touch menisci. (A. G. M. W.)

Cell Structure of Mamillary Body.—The mamillary body is well developed in all mammals. Medial, lateral, and dorsal nuclei can be distinguished. In the medial group some nuclei are better developed in lower, others in higher mammals. In the higher mammals the medial nucleus, probably equivalent to the medial and anterior nuclei of lower mammals, is better developed, whereas the basal and intermediate nuclei show a poorer development. In higher mammals the volume of the medial nuclear group, as a whole, shows a relative increase in association with that of the thalamus. The determination of volumes makes this relationship obvious. The lateral group of nuclei in all mammals bears a fairly constant relation to the volume of the mamillary body as a whole, as well as to the whole hypothalamus. The lateral nuclear group seems to have no connection with the thalamus. The dorsal nuclear group, well developed in lower mammals, undergoes a reduction in man and probably in the other higher mammals, whilst its volume decreases relative to the mamillary body, hypothalamus, and thalamus. It is probably not connected with the thalamus. (A. G. M. W.)

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The Magnesium Content of the Erythrocytes in Pernicious and Some Other Anemias. O. Bang and S. L. Orskov. 497.
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Studies in Iron Transportation and Metabolism. IV. Observations on the Absorption of Iron from the Gastro-intestinal Tract. C. V. Moore, W. R. Arrowsmith, J. Welch, and V. Minnich. 553.
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The Coagulation Defect in Hemophilia : the Clot-promoting Activity in Hemophilia of Berkefelded Normal Human Plasma free from Fibrogen and Prothrombin. E. L. Lozner, R. Kark, and F. H. L. Taylor. 603.
*The Occurrence of Abnormal Dark Adaptation and its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver. A. J. Patek and C. Haig. 609.

Acute Alcoholism.—Small doses of insulin did not affect the rate of disappearance of alcohol from the blood. Intravenous glucose produced an increased rate of fall in the blood alcohol only in severely intoxicated subjects, while insulin and glucose accelerated this fall in all intoxicated subjects. (J. N. C.)

Abnormal Dark Adaptation.—Abnormal dark adaptation was observed in patients with cirrhosis of the liver, and the changes were unrelated to jaundice. The administration of Vitamin A concentrates was followed by improvement, only partially maintained after the discontinuation of therapy. (J. N. C)

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*Creatinine in Mentally Defective Patients. L. S. Penrose and C. M. Pugh. 1151.
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*The Prognosis in Schizophrenia. Based on a Follow-Up Study of 129 Cases treated by Ordinary Methods. H. Stalker. 1224.
The Wassermann and Meinicke Klärungs Reactions (Original M.K.R.II and Ford Robertson-Colquhoun Modification) in the Diagnosis of Syphilis. An Analysis of 3,284 Parallel Tests. J. C. Thomas and W. M. Ford Robertson. 1241.
Sulphanilamide Therapy in Bacillary Dysentery. E. Jones and D. W. Abse. 1259.

Creatinine in Mental Defectives.—Slight creatinuria was found normal in mental defectives of both sexes. Creatinine excretion was high in cerebellar ataxia and in post-encephalitis lethargica. (B. McA.)

Prognosis in Schizophrenia.—50 per cent. of 129 schizophrenics treated between 1932 and 1937 were unimproved, 12 per cent. had had a complete remission, 17 per cent. had improved, and 21 per cent. had remitted and relapsed. Various aspects of the disease are discussed with regard to prognosis. (B. McA.)

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*Cerebral Lesions due to Vasomotor Disturbances following Brain Trauma. M. Helfand. 157.
Blood Pressure Changes during Insulin-shock Treatment. J. Pessin. 180.
*Physiochemical Mechanisms in Convulsive Reactivity. E. A. Spiegel and M. Spiegel-Adolf. 188.
Periodic Paralysis: Report of Two Fatal Cases. W. A. Smith. 210.
*Prolonged Non-Hypoglycemic Coma occurring during the Course of Insulin Shock Therapy. H. Freed and E. Saxe. 216.

Cerebral Lesions following Brain Trauma.—Microscopic and macroscopic examinations have been made in 22 cases of brain trauma in subjects that had no history of convulsions. The pathogenesis of white and red softening, traced microscopically, shows angio-necrosis secondary to tissue destruction in traumatic lesions. Lesions may be found in places other than the immediate site of injury. Some lesions in brain trauma are not accompanied by any visible change in the vessels, walls and the findings are attributed to functional disturbances of the vasomotor mechanism. (I. G. J.)

Physiochemical Mechanisms in Convulsive Reactivity.—The relationship between the excitability of nerve cells and the physiochemical state of the surface films is discussed. Abnormal convulsive reactivity is shown to be a part of this general problem. These workers investigated the changes in cellular permeability and polarization of brain tissue caused by anoxæmia, cerebral anæmia, raised intracranial pressure, increased hydration, alkalosis and acidosis, anæsthetics, and hypnotics. Epileptogenous agents act either by (*a*) a change produced in the ion concentration on the nerve cell surfaces—a convulsion occurring when threshold concentration is reached—or (*b*) a diminution in the density of the cellular surface films. Cell surfaces became more permeable and excitation is facilitated through lowering the threshold for metabolic and other stimuli. (I. G. J.)

Non-Hypoglycæmic Coma during Insulin Therapy.—Nine cases of prolonged non-hypoglycæmic coma following insulin shock treatment are reported, one of which showed subarachnoid hæmorrhage with recovery after the acute episode. The only chemical abnormality found was a depletion of the chlorides in the body fluids. This finding was an exaggeration of what occurs in insulin shock. The neurological picture is usually constant and the prognosis good. The authors suggest that the phenomena are due to reversible cellular changes in the hypothalamic region, and point out the similarity of the clinical features of hypothalamic lesions to those seen in prolonged non-hypoglycæmic coma. (I. G. J.)

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A Form of Congenital Myotonia in Goats. S. L. Clark, F. H. Luton, and J. T. Cutler. 297.
*The Reactions and Behaviour of Schizophrenic Patients treated with Metrazol and Camphor. B. Glueck and N. W. Ackerman. 310.
Induction of Seizures by Closing of the Eyes or by Ocular Pressure in a Patient with Epilepsy. L. J. Robinson. 333.
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A Case of Unilateral Torsion-Dystonia : a Clinico-Histological Study. R. Gordin. 344.
A Death associated with Metrazol Therapy : Report of a Case. R. M. Fellows and F. Koenig. 358.

Schizophrenics treated with Metrazol and Camphor.—A discussion of the psychodynamics of the treatment by convulsive agents. It is suggested that the somatic threat gives impetus to reintegration of the personality through the associated panic. (W. M. H.)

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Progressive Interstitial Hypertrophic Neuritis. P. Sloane. 429.
The Metrazol Seizure and its Significance for the Pathophysiology of the Epileptic Attack. H. Strauss, C. Landis, and W. A. Hunt. 439.
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*Observations on the Role of Vitamin B_1 in the Etiology and Treatment of Korsakoff Psychosis. K. M. Bowman, R. Goodhart, and N. Joliffe. 569.
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Studies in Delayed Awakening in Insulin Shock Therapy (Sakel). G. W. Robinson, G. J. Robinson, Jnr., and D. Feaster. 590.
The Hemato-Encephalic Barrier. M. M. Kessler, E. Moschcowitz, and N. Savitsky. 594.
Further Contribution to the Subject of Frontal Ataxia. A. Gordon. 614.

Vitamin B_1 and Korsakoff Psychosis.—In a group of cases of Korsakoff psychosis due to alcoholism subjects receiving thiamin showed incidence of recovery approximately seven times as great as those on a diet of borderline adequacy in vitamin B_1. The group was too small for the significance of the conclusion to be upheld statistically. (W. M. H.)

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A Comparison of the Thalamus in Dementia Præcox and Manic-Depressive Brains. R. J. Stein and L. H. Ziegler. 709.
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Does it befit Soviet Scientist to quote the Fascist "Scientists" ? I. Stilbans. 77.

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The Clinic and Pathology of Neurobroucellosis. E. M. Steblev. 19.
On the Question of the So-called Racial Characteristics in the Structure of the Cortex of the Large Hemispheres in Man. S. A. Sarkisov. 27.
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*Axons as Samples of Nervous Tissue. H. S. Gasser. 361.
*The Initiation of Impulses in Axons. J. Erlanger. 370.
Synaptic Mechanisms in Sympathetic Ganglia. An Analysis of Factors of Activity. D. W. Bronk. 380.
Transmission of Impulses through Cranial Motor Nuclei. R. F. de Nó. 402.
Problems of Synaptic Function. A. Forbes. 445.

Axons and Nervous Tissue.—Central positive potential evoked by antidromic volleys and associated subnormality have analogies in axons and peripheral endings. (W. M. H.)

Impulses in Axons.—The subthreshold effect of an action potential beyond a block at a node, seen in temporal summation, may be compared to the subthreshold effect of a shock applied to a fibre or of an action potential blocked at the neuromuscular junction by curare. (W. M. H.)

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*Further Observations upon the Release of Histamine by Skeletal Muscles. G. V. Anrep, G. S. Barsum, M. Talaat, and W. Wieninger. 240.
Use of the Dietary Anœstrous Adult Rat for the Assay of the Œstrus-inducing Gonadotrophic Substance. R. D. H. Heard and S. S. Winton. 248.
*Acetylcholine Synthesis in a Sympathetic Ganglion. G. Kahlson and F. C. MacIntosh. 277.
*The Apparent Augmentation of Pituitary Antidiuretic Action by Various Retarding Substances. R. L. Noble, H. Rinderknecht, and P. C. Williams. 293.
Central Action of Anticholinesterases. A. Schweizer, E. Stedman, and S. Wright. 302.
The Effect of the Hydrogen-Ion Concentration on the Stability of the Antidiuretic and Vasopressor Activities of Posterior Pituitary Extracts. H. Heller. 337.
*The Peripheral Action of Tetanus Toxin. A. M. Harvey. 348.

Release of Histamine by Skeletal Muscles.—Histamine released from skeletal muscle during contraction comes from a pre-existing store. Contraction of muscle after complete degeneration of its nerves releases a comparable amount of histamine. During the early stage of degeneration there is a small continuous output of histamine. (W. M. H.)

Acetylcholine Synthesis in Sympathetic Ganglion.—When perfused with solution containing only inorganic salts the superior cervical ganglion fatigues rapidly and the acetylcholine output on stimulation diminishes. This fatigue is removed by glucose mannose, galactose, lactate, or pyruvate, all of which promote acetylcholine synthesis. Fructose, sucrose, lactose, arabinose, d-l glyceraldehyde, acetate, acetoacetate, succinate, and acetaldehyde have no effect. (W. M. H.)

Pituitary Antidiuretic Action.—Various cations, anions, and organic substances when added to posterior pituitary extract prolong the antidiuresis obtained by subcutaneous injection. The importance of pure extracts in assays of antidiuretic potency by subcutaneous injection is emphasized. (W. M. H.)

Peripheral Action of Tetanus Toxin.—Local muscular rigidity may be produced by local injection of tetanus toxin. Such muscle shows a diminished response to maximal nerve excitation, but normal potentiation of twitches following a period of tetanic stimulation. The response to a single nerve volley is repetitive in nature. The contraction on injection of acetylcholine is followed by a prolonged increase in tension. Eserine has little potentiating effect on the nerve twitch tension. The action of the tetanus toxin would appear to be in the region of the neuromuscular junction. (W. M. H.)

Vol. 96. No. 4. September 1939.

A Comparative Study of the Effect of the Interaction of Ions, Drugs, and Electrical Stimulation as Indicated by Contraction of Unstriated Muscle. I. Singh. 367.
*Properties of the Substance liberated by Adrenergic Nerves in the Rabbit's Ear. J. H. Gaddum and H. Kwiatkowski. 385.
*The Effect of Monosaccharides on Water Absorption from the Subarachnoid Space. T. H. B. Bedford. 392.

Substance liberated by Adrenergic Nerves of Rabbit.—When the adrenergic nerves of the perfused rabbit's ear are stimulated the effluent contains a substance which stimulates the frog's heart and constricts the vessels of the rabbit's ear. Assays of adrenaline equivalent by these methods agree with colorimetric estimates by Shaw's method. (W. M. H.)

Monosaccharides and Water Absorption from Subarachnoid Space.—Isotonic solutions of glucose, xylose, and mannose all fail to alter the rate of absorption when introduced into the subarachnoid space. There is evidence of specific absorption of glucose. (W. M. H.)

Vol. 97. No. 1. November 1939.

The Effect of Noxious Agents on Creatine, Creatinine, Chloride, and Water Excretion. J. S. L. Browne, S. Karady, and H. Selye. 1.
*The Quick Component of Nystagmus. A. K. McIntyre. 8.
*The Blood Flow through Muscle during Sustained Anhydrase. H. Barcroft and J. L. E. Millen. 17.
Gastric Carbonic Anhydrase. H. W. Davenport. 32.
*Responses which Nerve Impulses evoke in Mammalian Striated Muscles. J. C. Eccles and W. J. O'Connor. 44.
The Effect of Choline on the Fatty Liver of Carbon Tetrachloride Poisoning. H. M. Barrett, C. H. Best, D. L. MacLean, and J. H. Ridout. 103.
Diet and the Insulin Content of Pancreas. C. H. Best, R. E. Haist, and J. H. Ridout. 107.
Ketonæmia in Pregnant Ewes and its Possible Relation to Pregnancy Disease. A. H. H. Fraser, W. Godden, L. C. Snook, and W. Thomson. 120.
The Occurrence of Ovulation in the Rabbit as a Result of Stimulation of the Central Nervous System by Drugs. F. H. A. Marshall, E. B. Verney, and M. Vogt. 128.

Quick Component of Nystagmus.—In cats under light narcosis the tonic discharges of impulses in the 6th nerve is not altered after cutting the nerve distally. The rhythm of normal nystagmus produced by labyrinthine stimulation likewise appears independent of impulses from the ocular muscles, for the characteristic impulses in the 6th nerve persist after section of the 3rd, 4th, and 6th nerves and extirpation of retractor bulbi. (W. M. H.)

Blood Flow through Muscle during Sustained Anhydrase.—Changes in temperature in the muscles of the leg in man were taken as indices of changes in blood flow on contraction, the temperature having first been stabilized at *c.* 39·5° C. or 34·5° C. by immersion. 0·05 and 0·1 maximal contractions give marked hyperæmia; 0·2 and 0·3 maximal contractions are not accompanied by hyperæmia. Compression of vessels by taut muscle fibres is believed to suppress hyperæmia. (W. M. H.)

Nerve Impulse Responses evoked in Striated Muscle.—Responses in the motor and plate and in the soleus fibre have been studied after successive nerve impulses. The earliest second impulse (at *c.* 0·65–1·0 sec.) that can be set up in the motor nerve fibre gives rise to a negative potential of the motor and plate region relative to the rest of the muscle. The latent period of this potential diminishes at longer impulse intervals, but it may be preceded slightly by the new-born muscle impulse, which occurs at impulse intervals of *c.* 1·6–1·9 sec. The end plate potential appears independent of the new-born impulses, but aids in their growth when it is sufficiently delayed. (W. M. H.)

PHYSIOLOGICAL REVIEWS

Vol. 19. No. 4. October 1939.

The Effect of Toxæmia on Metabolism. E. Holmes. 439.
The Present Status of the Barbiturate Problem. A. L. Tatum. 472.
Muscle Hemoglobin. G. A. Millikan. 503.
The Architecture of Viruses. W. M. Stanley. 524.
Fat Transport in the Animal Body. W. R. Bloor. 557.

PSYCHIATRIC QUARTERLY

Vol. 13. No. 4. October 1939.

Some Unconscious Determinants in Homicide. P. R. Lehrman. 605.
Psychiatry and the Law—Co-operators or Antagonists? W. Overholser. 622.
The Blood-Cerebrospinal Fluid Barrier of Normal Children as determined by the Bromide Permeability Quotient. F. A. Mettler, M. Robinaw, W. R. Brown, and C. McK. Burpee. 639.
Humor and Hypomania. I. H. Coriat. 681.
Depression as the Chief Symptom. L. H. Ziegler. 689.
A Method for Differentiating Manic-Depressive Depressions from Other Depressions by Means of Parotid Secretions. E. I. Strongin and L. E. Hinsie. 697.
The Christian Formulation and Medicine. S. E. Jeliffe. 705.
The Value of Diphenyl Hydantoinate (Dilantin) in Psychoses with Convulsive Disorders. N. D. Black. 711.
A Contribution to the Problem of Alcoholic Deterioration. J. J. Dorey, W. Hamburger, and R. B. Sampliner. 721.
Personality in Alcoholic Disorders: Acute Hallucinosis and Delirium Tremens. N. J. T. Bigelow, S. R. Lehrman, and J. N. Palmer. 732.

REVUE NEUROLOGIQUE

Vol. 72. No. 1. July 1939.

Adénome Basophile de l'Hypophyse. (Basophil adenoma of the pituitary.) A. Austregesilo. 1.

Fibrolipome Intradural de la Moelle. (Intradural fibrolipoma of the cord.) J. Jabotinski. 15.

Oligodendroblastome Intéressant le Corps Calleux, Considérations sur le Syndrome du Corps Calleux. (Oligodendroblastoma involving the corpus callosum : the callosal syndrome.) O. Sager and I. Bazgan. 32.

Vol. 72. No. 2. August 1939.

Étude Anatomique et Pathogénique des Tumeurs Cérébrales Métastatiques. (Pathogenetic and anatomical study of metastatic cerebral tumours.) H. Roger, L. Cornil, and J. E. Paillas. 137.

Chorées Prolongées. (Persistent chorea.) L. Babonneix and P. Guilly. 149.

Contribution à l'Étude de la Physiopathologie des Lobes Frontaux. (Contribution to the study of the physiopathology of the frontal lobes.) L. Barraquer. 160.

À Propos d'un Cas de Dysostase Cranio-Faciale Héréditaire et Familial. (A case of hereditary and familial cranio-facial dysostosis.) A. Austregesilo and A. Borges Fortes. 165.

Metastatic Tumours of Cerebrum.—A summary of their histological features and modes of spread. (W. M. H.)

Vol. 72. No. 3. September 1939.

Hypertrophie Musculaire Généralisée du Nourrisson et Hypothyroïdie Congénitale (Syndrome de Debré-Semelaigne). (Generalized muscular hypertrophy and congenital hypothyroidism in the infant : Debré-Semelaigne's syndrome.) H. Darré, P. Mollaret, Mme. Zagdoun, and Mlle. Oehmicen. 249.

Hypertrophie Musculaire sans Myotonie chez un Nourrisson de 7 Mois avec Retard Général de Développement par Hypothyroïdie Congénitale (Syndrome de Debré-Semelaigne). Examen Electrique. (Muscular hypertrophy, developmental retardation, and congenital hypothyroidism in a 7-month baby.) G. Bourguignon. 282.

Le Problème de l'Évolution Maligne de la Tumeur Royale dans une Maladie de Recklinghausen à Caractère Familial. (Malignancy in Recklinghausen's disease.) R. Huguenin, S. Burgi, and J. Baret. 287.

RIVISTA DI NEUROLOGIA (NAPOLI)

Vol. 12. No. 4. August 1939.

*Difficoltà Diagnostiché in Casi di Tumore Endomidollare. (Difficulties in diagnosis in cases of endomedullary tumours.) A. Paleari. 269.

*Simpatoma Embrionario Benigno Plurinodulare Sottocutaneo. (Benign sympathetic neuroblastoma with multiple subcutaneous nodules.) P. Brusa and N. Orlandi. 291.

*Cerebellite da Parotite Epidemica. (Inflammation of the cerebellum in mumps.) G. Glück. 309.

Diagnosis of Endomedullary Tumours.—Two cases are described which showed a slow course, spontaneous remissions, and identical histological findings. In the first there was an initial acute phase due to a leutic pachymeningitis followed by a long period of health, but subsequent death from a glioma. In the second there was an apoplectiform initiation, presumably due to a hæmatomyelia, followed by a remission when this was absorbed and final death from a neoplasm. These cases illustrate how the history and course may obscure the diagnosis of tumour. (R. G. G.)

Benign Sympathetic Neuroblastoma.—A clinical and histopathological illustration of a very rare case of sympathetic neuroblastoma characterized by multiple subcutaneous nodules and by a benign course. The case of an infant is described which had presented for about 4 years, beginning with the first week of life, numerous small subcutaneous tumours, widely disseminated and varying in size from that of a pea to that of a nut. These neoplasms after a variable number of months, according to the size which they reach, regress so as to disappear without leaving the least trace or in any way interfering with the development of the child, which has and still does enjoy the best of health. The structure of these tumours, studied at three different periods of their evolution, show a proliferation of the immature elements of the sympathetic. The authors interpret this case as a hyperplastic process of the subcutaneous ramifications of the sympathetic superimposed on a basis of congenital malformation. (R. G. G.)

Inflammation of Cerebellum in Mumps.—Towards the end of an attack of mumps a sudden onset of severe cerebellar symptoms was presumably due to an extensive cerebellar hæmorrhage. Since this case and most others of encephalitis complicating mumps get better, the pathology is obscure, but it would appear that the lesion is vascular and the clinical picture due to hæmorrhages. (R. G. G.)

Vol. 12. No. 5. October 1939.

*Epilessia ed Afasia Riflessa da Ascesso Polmonare. (Epilepsy and reflex aphasia in a case of pulmonary abscess.) F. Vizioli. 317.
*Sull'Impiego del Pneumoencefalo nella Meningite Cerebrospinale Epidemica. (The injection of air into the subarachnoid space and ventricles in meningococcal meningitis.) G. Murano. 336.

Epilepsy and Reflex Aphasia in Pulmonary Abscess.—The clinical observations described by the authors deal with a patient who developed, during the course of a pulmonary abscess, epileptic convulsions, psychical disturbances, and a motor aphasia, all of which recovered in a relatively short time without leaving any important residual effects. Apart from the aphasia, which the literature shows to be an extremely rare event as a complication of pleural or pulmonary disease, the case is shown to be of considerable interest in view of the diagnostic possibilities to which the symptomatology here described might give rise. The different theories (toxic, infective, reflex, or embolic) which have been proposed as a pathological interpretation of the epileptic and other nervous manifestations which can be identified in patients with pulmonary and pleural disease are referred to and discussed. The authors conclude, on clinical and pathological grounds, that in the case described both the aphasia and the epilepsy are best accounted for on a reflex basis. (R. G. G.)

Air Injection into Subarachnoid in Meningitis.—After the good therapeutic results obtained by the injection of air into the spinal theca in five cases of cerebrospinal fever which have already been described in a previous paper (*La Pediatria*, **2**, 1939) the author has continued systematically to adopt this treatment in all cases of meningococcal meningitis which have come under his care. The results obtained (seven children completely cured), which have been correlated very carefully with the various factors already known to influence the prognosis and outcome of this disease, are such as to demonstrate the real advantages resulting from the adoption of such therapeutic measures in the treatment of meningococcal meningitis. After having once again shown how the introduction of sterile air into the spinal theca can restore and maintain the patency of the foramina connecting the ventricles and the subarachnoid space, and so facilitating the drainage of purulent C.S.F., the author has proceeded to study the possible variations in function produced by the contact of the ventricular ependyma and the choroid plexus with the air. These investigations show that the blood—C.S.F. barrier—becomes more permeable when air is present in the ventricles of healthy subjects, and that this is also the case in meningitis. This fact is of great importance in ensuring the therapeutic efficiency of both the serum and sulphanilamide in common use in the treatment of meningococcal meningitis. (R. G. G.)

SCHWEIZER ARCHIV FÜR NEUROLOGIE UND PSYCHIATRIE

Vol. 44. No. 1. 1939.

Die "undendliche Analyse" Freud's. (Freud's. "unending analysis.") R. Markuszewicz. 1.
Die "undendliche Analyse" Freud's. Bemerkungen zum gleichnamigen Aufsatz von R. Markuszewicz. (Freud's "unending analysis." Remarks on the article of that name by Markuszewicz.) E. Bibring. 25.
Monoplegie der Finger und taktile Agnosie. Zur Klinik eines cerebralen Gefäss-syndroms. (Finger monoplegia and tacile agnosia. A clinical study of a cerebral vascular syndrome.) L. Halpern. 35.
Über die Alkoholhalluzinose und ihre Beziehungen zur Schizophrenie. (Alcohol hallucinosis and its relationship to schizophrenia.) K. Huber. 43.
Anormalenzahlung im Kanton Appenzell A.Rh. vom Jahre 1937. Bearbeitet im Auftrage der amtlichen Zählkommission. (Number of abnormals in Canton Appenzell in 1937, studied from the employment census.) A. Koller. 69.
Die Psychoanalyse und die menschlichen Existenzprobleme. (Psychoanalysis and the problem of human existence.) A. Storch. 102.
Relazione tra differenziazione strutturale e funzionale dei centri e delle vie nervose nell'embrione di pollo. (Relationship of structural and functional differentiation of the nervous centres and pathways in the chick embryo.) F. Visintini and R. Levi-Montalcini. 119.
Über Verknöcherung der Aderhautgeflechte. (Thickening of vessel walls.) G. Will. 151.

ZEITSCHRIFT FÜR DIE GESAMTE NEUROLOGIE UND PSYCHIATRIE

Vol. 166. No. 4. July 1939.

*Die Astrocytome der Oblongata, Brücke und des Mittelhirns. (Astrocytomas of the medulla, pons, and midbrain.) O. Foerster and O. Gagel. 497.
Beiträge zur normalen und pathalogischen Anatomie des Rückenmarks. III. Diffuse Angioneuromatose des Lendenmarks und seiner Pia. (Contributions to the normal and pathological anatomy of the spinal cord. III. Diffuse angioneuromatosis of the lumbar cord and its pia.) M. Staemmler. 529.
*Über experimentelle Cardiazolepilepsie. (Experimental cardiazol epilepsy.) P. O. Andrell and S. Hansson. 537.
*Einige Stoffwechseluntersuchungen bei endogenen Psychosen mit besonderer Berücksichtigung der Leberfunktion. (Some metabolic studies in endogenous psychoses, with some consideration of liver function.) G. Lundquist. 546.
Bisherige Ergebnisse über den Phosphatidstoffwechsel im Liquor cerebrospinalis. I. Bericht über ein neues Extraktionsverfahren für kleinste Liquor-

mengen. (The present position of phosphatid metabolism in the cerebrospinal fluid. I. A new extraction method for smallest quantities of fluid.) F. Roeder. 557.

* Die Schwefelkohlenstoffvergiftung der Nervensystems. (Carbon disulphide poisoning of the central nervous system.) C. Baumann. 568.

Versuch einer Cardiazolbehandlung der Epilepsie- (Cardiazol in the treatment of epilepsy.) A. Erb and J. Poźniak. 581.

Eine weitere Verbesserung meiner Markscheidenfärbemethode am Gefrierschmitt. (A further improvement in my method for staining myelin sheaths in frozen sections.) K. Schroeder. 588.

Beitrag zur Auswahl der Behandlungsmethode bei der Schizophrenietherapie. (The choice of method of treatment in schizophrenia.) R. Elste. 594.

Behandlung Schizophrener mittels Insulin- oder Konvulsions-shocks ? Klinischer Beitrag für die Auswahl der Kranken. (The treatment of schizophrenia by insulin or convulsion shock. A clinical contribution on the choice of patient.) A. Silveira. 604.

*Experimentelle Untersuchungen über die lokale Einwirkung des Thiophens im Zentralnervensystem. (Experimental investigation of the local action of thiophen in the central nervous system.) T. Upners. 623.

Experimentelle Untersuchungen über retrograde Zellveränderungen in der unteren Olive nach Läsionen des Kleinhirns. (Experimental studies of retrograde cell changes in the olivary body after cerebellar lesions.) A. Brodal. 646.

Astrocytomas of the Medulla.—In 25 histologically verified tumours of this region 12 were astrocytomas. In six cases the patient was under 20. The average duration of symptoms was 3 years 3 months. The tumours were diffuse in four cases, three of these being in the older group. Four tumours were circumscribed, one having the structure typical of a solid cerebellar astrocytoma. Some were protoplasmic astrocytomas not different from those in the cerebrum. A piloid astrocytoma showed in parts a resemblance to a polar spongioblastoma. In only one case was there cystic formation. (G. M. G.)

Experimental Cardiazol Epilepsy.—Histological studies were made of the brains of twelve guinea-pigs after repeated fits induced by cardiazol. No changes could be found which could be ascribed to the cardiazol. (G. M. G.)

Metabolic Studies in Endogenous Psychoses.—The author criticizes reports of disordered liver function and other changes in mental disease on the basis of isolated investigations. So in groups of old-established schizophrenics, young recent cases, depressions, and other conditions patients were kept in bed on standard diets and various studies made at 3-hourly intervals for at least 3 days, to see if any significant rhythmic variations were to be found. Temperature, urine output, urobilin, urine colour values, urea, and serum albumen were investigated. In some cases Rona's test for quinine-resistant lipase was studied and in some blood pigment values. Some curves were obtained but were not consistent or significant, and the results give no confirmation of any disorder of liver function. (G. M. G.)

Thiophen Poisoning.—In experimental chronic poisoning in dogs a selective effect on the cerebellum is produced. In milder cases a diffuse change in the granulosa is found. In the more severely affected cases there are localized areas of degeneration and gliosis in the granulosa and to a less extent in the Purkinji cells, the distribution showing that the poison acts through a circulatory disturbance. The sensitiveness varies with the age, the older dogs showing quicker and more severe toxic symptoms. (G. M. G.)

BOOK REVIEWS

ANALYSIS OF HANDWRITING

H. J. Jacoby

(George Allen and Unwin, Ltd., London. 1939. Pp. 312. 10*s.* 6*d.*)

The psychiatrist, eager for aids in the study of personality, may often have remarked on the paucity of reliable books in English on the analysis of handwriting. He may rightly look for one in which the principles of graphological interpretation are induced from the correlation of writing characteristics with the features of personality adequately studied and assessed. Rated by such a criterion the present volume does not go far in meeting a real demand. It is an introduction to graphology and at points perhaps necessarily superficial. Some of its limitations are self-imposed —thus the neurological aspects of calligraphy are scarcely mentioned ; other drawbacks and more serious come from the poor presentation of data on personality. The results of the " psychological penetration " of the author are loosely expressed in quite unorthodox jargon. The reader longs for adequate clinical description of the make-up of the subjects ; he asks for something more certain than astral conceptions like " spiritual deflation of the ego." Still, the volume has much of real value and compliments will surely be forthcoming from mail censors. The format is good and the accessibility of text and sample references commendably easy.

AN OUTLINE OF MEDICAL PSYCHOLOGY

E. Fretson Skinner

(H. K. Lewis and Co., Ltd., London. 1939. Pp. 174. 6*s*.)

Dr. Skinner, in the introduction to his book, states that " the present essay is an attempt to place before the non-technical reader and medical students entering their professional curriculum some of the facts and hypotheses of modern psychology as applied to the causation of nervous diseases and their treatment by its means." Parts II and III, which deal with psychopathology and clinical aspects of psychiatry, adequately fulfil his purpose. Part I is a brief biological sketch which might well be named " Facts of life and nature for the very young." " In the hen, however, the male elements, the spermatozoa, are actually deposited in the female ovary canal before the egg is laid. The cock bird deposits his seed in the hen as the result of some attraction exerted by the hen bird probably due to chemical substances manufactured by her." It is difficult to understand the author's purpose in serving up forty pages of this sort of stuff to those who are likely to read a book, however elementary, on medical psychology.

INJURIES OF THE NERVOUS SYSTEM, INCLUDING POISONINGS

Otto Marburg and Max Helfand

(Veritas Press, Inc., New York. 1939. Pp. 213. $3.00.)

With the enormous increase in injuries to the nervous system that is bound to occur during wartime, a book dealing with their diagnosis and treatment is certain to be welcomed. It is a pity, therefore, that this book should be marred by the manner of its presentation. The material is excellent, but it is only too plain that a considerable part of the book has been written by someone with an incomplete grasp of the English language. There are also a number of misprints and numerous mistakes in the spelling of authors' names both in the text and in the list of references at the end of the book. The classification, symptoms, signs, and pathology of the various injuries have been well described, but for the most part treatment has not been given in sufficient detail. The chapters on head injuries are good, but the part played by litigation in post-concussional neurosis is not sufficiently stressed. The section on spinal cord injuries is excellent, that on poisons poor. Some of the illustrations could easily be improved.

TEXTBOOK OF NERVOUS DISEASES

Robert Bing

(Translated and enlarged by Webb Haymaker. Henry Kimpton, London. 1939. Pp. 838. 50*s*.)

This is the first English translation of this book which appeared in its original form in 1913. It covers practically the whole field of neurology and in addition there are three chapters on the psychoneuroses. The author has produced a most clear and logical account of the subject and the translation is most skilfully done, the book reading very fluently throughout, although one is bothered at times by the footnotes which seem rather too frequent. Treatment is very fully dealt with, in some cases too fully, for so many methods are given that one is at a loss to know which to use. But perhaps this is a fault of neurology rather than the book. The numerous photographs are good and show what they are meant to show and in addition there are some very helpful diagrams illustrating various anatomical points. A complete bibliography at the end of each chapter should prove very helpful.